A detailed investigation into potential genes and their variants regulatory sequences causing endometriosis and how the environment may impact upon these.

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Abstract

Introduction

Endometriosis is an inflammatory and chronic gynaecological condition leading to infertility and severe chronic pelvic pain. Although effecting 10% of women worldwide, there is limited knowledge on the aetiology and pathophysiology of the disease. Research into the condition has shown that a woman is 10 times more likely to develop endometriosis if a close family member (e.g., mother or sister) has also been diagnosed. These observations suggest that endometriosis may have a genetic component. The aim of this project was to carry out a detailed investigation of genetic factors and their interactions with the environment (e.g. EDCs) which potentially predispose an individual to endometriosis development.

Methods

A combination of a literature review and data interrogation in the Genomics England 100,000 genomes project were undertaken to identify endometriosis-related genetic loci that could be susceptible to environmental pollutants.

Results

57 genes were identified to have a role in increasing the risk of endometriosis development. The incidence of potentially pathogenic variants of these 57 genes was explored through data analysis from the Genomics England 100,000 genome database. Five genes and associated variants were identified in women affected by endometriosis that were also sensitive to environmental insults. These were *CNR1*, *IL-6*, *IDO1*, *KISSR1*, and *TACR3*. EDCs are commonly found as part of cosmetics and other personal care items routinely used by women.

Conclusion

The findings of this project suggest that a genetic susceptibility to developing endometriosis could be exacerbated by the presence of environmental pollutants.

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List of abbreviations

Abbreviation	Meaning	Page
DIE	deeply infiltrating endometriosis	23
IBS	irritable bowel syndrome	25
IVF	in vitro fertilisation	26
PID	pelvic inflammatory disease	27
MRI	magnetic resonance imaging	28
ESHRE	European society of human reproduction and embryology	29
Gn-RH	Gonadotropin-releasing hormone	30
ORS	ovarian remnant syndrome	31
ICAM-1	intercellular adhesion molecule 1	32
EDCs	Endocrine disrupting chemicals	32
SNPs	single nucleotide polymorphisms	33
SRP14	signal recognition particle 14	34
BMF	Bcl-2-modifying factor	34
GDAP1	Ganglioside Induced Differentiation Associated Protein 1	34
MLLT10	Mix-lineage leukemia translocated to 10	34
BSN	Bassoon Presynaptic Cytomatrix Protein	34
NGF	nerve growth factor	34
GE	Genomics England	36
NHS	National Health Service	36
GERN	Genomics England Research Network	36
WOS	Web of Science	38
IDO1	Indoleamine 2,3-dioxygenase 1	42
IL-6	Interleukin 6	42
CNR1	cannabinoid receptor 1	42
TACR3	tachykinin receptor 3	42
KISS1R	KISS1 receptor	42
TCDD	2,3,7,8-Tetrachlorodibenzodioxin	42
DEHP	Di-(2-ethylhexyl) phthalate	42
HPGA	hypothalamic-pituitary-gonadal axis	42
GnRH	Gonadotropin hormone-releasing hormone	42
IDO1-KYN-AhR	IDO1-Kynurenine-Aryl hydrocarbon receptor	44
NIH	national library of medicine	44
PE	participant explorer	44
IVA	interactive variant analysis	44
SNVs	single nucleotide variations	47
INDEL's	insertion-deletion mutations	47
$\chi 2$	Chi-squared test	49
Df	degree of freedom	49
BH	Benjamini-Hochberg	50
rsID	Reference SNP ID number	50
ClinVar	Clinical Variation	50
dbSNP	Database of SNPs	50
UCSC	University of California, Santa Cruz genome browser	50
COMT	catechol-O-methyltransferase	54

CDKN2B-AS1	**cyclin-dependent kinase inhibitor 2B antisense RNA 1**	**54**
KRAS	**Kirsten Rat Sarcoma viral oncogene homolog**	**54**
PDZRN3	**PDZ domain containing ring finger 3**	**55**
PTPRD	**protein tyrosine phosphatase receptor type D**	**56**
TNF-a	**tumor necrosis factor alpha**	**56**
IL1-b	**interleukin 1 beta**	**56**
IL1A	**interleukin-1 alpha**	**56**
NFE2L1	**nuclear factor erythroid 2-like 1**	**56**
CEP112	**centrosomal protein 112**	**55**
MFHAS1	**malignant fibrous histiocytoma-amplified sequence 1**	**55**
SLC35G6	**solute carrier family 35 member G6**	**55**
KDR	**kinase insert domain receptor**	**55**
FN1	**fibronectin 1**	**55**
IFNG	**interferon gamma**	**55**
TNKS	**Tankyrase**	**55**
TAC	**Tachykinin precursor**	**55**
KISS1	**KiSS-1 Metastasis Suppressor**	**55**
SKAP1	**Src kinase-associated phosphoprotein 1**	**55**
ETAA1	**Ewing tumor-associated antigen 1**	**55**
ARL14EP	**ADP ribosylation factor like GTPase 14 effector protein**	**55**
NAT2	**N-acetyltransferase 2**	**55**
RND3	**Rho family GTPase 3**	**55**
SCAF11	**SR-related CTD associated factor 11**	**55**
TFAP2D	**transcription factor AP-2 delta, or activating enhancer binding protein 2 delta**	**55**
ZNF536	**zinc finger protein 536**	**55**
PI3K	**phosphatidylinositol-3 kinase**	**55**
CDC42	**cell division cycle 42**	**55**
ARID1A	**AT-rich interaction domain 1A**	**56**
KITLG	**KIT ligand**	**56**
SMAD3	**SMAD family member 3**	**56**
KIF3A	**kinesin family member 3A**	**56**
MAPK	**mitogen-activated protein kinase**	**56**
ESR1	**estrogen receptor 1**	**56**
FSHB	**follicle stimulating hormone subunit beta**	**56**
GREB1	**growth regulating estrogen receptor binding 1**	**56**
PGR	**progesterone receptor gene**	**56**
CYP17A1	**cytochrome P450 family 17 subfamily A member 1**	**56**
NKB3R	**neurokinin B receptor**	**56**
WNT4	**wingless-type MMTV integration site family, member 4**	**56**
VEZT	**vezatin, adherens junctions transmembrane protein**	**56**
TRIM32	**Tripartite motif-containing protein 32**	**56**
KLF3	**Krüppel-like factor 3**	**56**
ID4	**Inhibitor of Differentiation 4**	**56**
LMO7	**LIM domain only protein 7**	**56**
MDM2	**murine double minute 2**	**56**
NFE2L3	**nuclear factor, erythroid 2-like 3**	**56**
PARP11	**poly(ADP-ribose) polymerase family member 11**	**56**
PRIM2	**DNA primase subunit 2**	**56**

RABGAP1L	RAB GTPase activating protein 1	56
CBX1	chromobox 1	57
CYP2C19	cytochrome P450 family 2 subfamily C member 19	57
GSTM-1	glutathione S-transferase mu 1	57
BPA	Bisphenol A	63
TBBPA	Tetrabromobisphenol A	63
DiNP	diisononyl phthalate	63
FSHR	follicle-stimulating hormone receptor	65
KYN	kynurenine	66
L-Trp	L-tryptophan	65
NFK	Nuclear factor kappa B	66
ECS	endocannabinoid system	65
CD163	scavenger receptor cysteine-rich type 1	66
SCD163	soluble CD163	66
MYH9	non-muscle myosin heavy chain type a	66
GPCR	G protein-coupled receptor	66
JNK	c-Jun N-terminal kinase	68
P-CSMS	phosphatidylinositol-calcium second messenger system	69
TF	Transcription factor	81
ZIC2	Zic family member 2	81
ZNF707	Zinc finger protein 707	82
ZBTB11	Zinc finger and BTB domain-containing protein 11	82
ZNF701	Zinc finger protein 701	83
SOX4	SRY-box transcription factor 4	83
SOX6	SRY-box transcription factor 6	83
FOXD3	Forkhead box D3)	83
SOX11	SRY-box transcription factor 11	83
SOX12	SRY-box transcription factor 12	84
PVC	polyvinyl chloride	104
E2	estradiol	105
SHP-1	Src homology region 2 domain-containing phosphatase-1	106
ITIM	immunoreceptor tyrosine-based inhibitory motifs	106
IFN-γ	interferon gamma	107
NK	natural killer	108
CD4+	cluster of differentiation 4	108
ECC	endometrial cancer cells	108
lncRNA	Long non-coding RNA	108
SNHG12	Small Nucleolar RNA Host Gene 12	108
TH2	T helper 2	112
G-protein	guanine-nucleotide-binding protein	113
ERKs	extracellular signal-regulated kinases	117
PCB	polychlorinated biphenyl	117
ESC	embryonic stem cells	117
GWAS	genome-wide association studies	119
Ov-CAA	ovarian clear cell adenocarcinoma	119
RT-PCR	reverse-transcription polymerase chain reaction	122
MMPs	matrix metalloproteinases	189
AMH	anti-Mullerian hormone	190

TGF-β	transforming growth factor–β	191

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Declaration

I can confirm that the work presented in this study is my own.

Amelia Jane Warren.

1.0 Introduction

1.1 Endometriosis and female fertility

Endometriosis is a gynaecological condition described as heterogenous and estrogen dependent, meaning endometriotic cells develop on organs other than the inside of the uterus, under estrogens control. Endometriosis is characterised by chronic inflammation of the pelvis, and presence of scar tissue from implanted endometrial cells on organs separate from the uterus (e.g., ovaries, fallopian tubes) (Angioni et al., 2020). Endometriosis affects approximately 10% of reproductive age women globally (Kanellopoulos et al., 2022). Endometriosis onset is usually seen during puberty, when menstruation starts, regressing at menopause (Taylor et al., 2021). Endometriotic cells are dysregulated through estrogens influence on expression of anti-apoptotic genes. This prevents endometrial cells implanted on organs outside the uterus from entering cell death cycles, enabling and enhancing their survival (Kokike et al. 2015).

Endometriosis is categorised in four stages (see figure 1) by the American Society of Reproductive medicine (Zhang et al., 2019). Stage 1 is classified as minimal with superficial endometrial cell implantation leading to shallow lesions on areas of the pelvis (Koninckx et al., 2022). Stage 2 is classified as mild with more implants than stage 1 and deeper in the abdominal wall with possible scar tissue (Grigore et al., 2017). Stage 3 is classified as moderate with deep implants and thick bands of scar tissue (Mikhaleva et al., 2020). Stage 4 is classified as severe, widespread multiple deep implants, thick adhesions, and large cysts (Cohen et al., 2018). The clinical manifestations related to each 4 stages are summarised in Table 1.

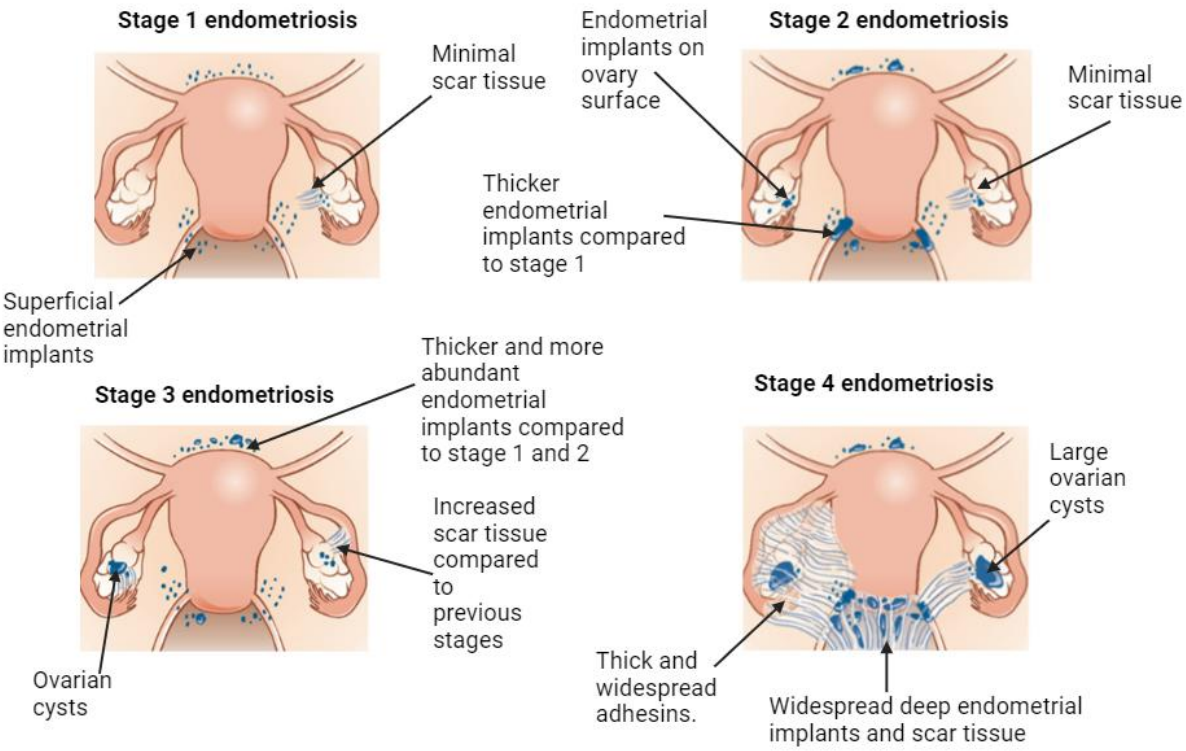

Figure 1: Adapted from Barbieri, 2016 demonstrates endometriosis progression within each stage of endometriosis. The blue dots represent endometrial implants which can be seen to increase and thicken as the stage and severity of endometriosis increases. The blue lines indicate scar tissue which are seen to become deeply infiltrating and more abundant as the stage of endometriosis increases.

Table 1: The 4 stages of endometriosis and associated clinical manifestations.

Endometriosis stage	**Clinical manifestation**
1 or minimal	Occurs in approximately 80% of women diagnosed with the condition and is generally associated with superficial endometrial cell implantation within the membrane lining of the peritoneum and abdominal cavity. This causes formation of shallow lesions on areas of the pelvis, abdomen, and organs associated within the abdominal cavity (Koninckx et al., 2022).
2 or mild	Associated with the presence of a larger number of endometrial implants, compared to stage 1. These implants can be found in deeper abdominal layers, possibly combined with some scar tissue (Grigore et al., 2017).
3 or moderate	Presence of many deep implants and/or small cysts on one or both ovaries, combined with thick bands of scar tissue (adhesions). Ovarian endometriosis (chocolate cysts) occurs between 17%-44% of all endometriosis cases and are filled with dark fluid stemming from ectopic endometrial tissue. These occur mainly in the ovaries but can be present within the pelvis and abdomen. They are

	characterised through a higher fibrous tissue content in comparison to normal haematomas due to the cystic lesions occurring through endometriosis and can lead to a higher risk of ovarian cancer (Mikhaleva et al., 2020).
4 or severe	Widespread multiple deep implants, thick adhesions, and large cysts on one or both ovaries present. Deeply infiltrating endometriosis (DIE) is the most uncommon form of endometriosis occurring in between 1-5% of patients. This is the most severe form of endometriosis as the endometrial tissue located in the peritoneum exceeds 5mm in depth leading to scarring of the organs, inflammation and organs moving and locking into incorrect positions. This occurs when the endometrial tissue located outside of the uterus implants into adjacent tissue occupying organs and areas which are condensed with nerves (Cohen et al., 2018).

Growth and alteration of endometrium is affected during the menstrual cycle, in response to sex steroid hormone changes (Cindrova-Davies et al., 2021). Hormones fluctuate during the menstrual cycle (McNulty et al., 2020) (figure 2). However, endometriosis patients' estrogen is consistently higher than progesterone from estrogen dominance and progesterone resistance (Fukui et al., 2019).

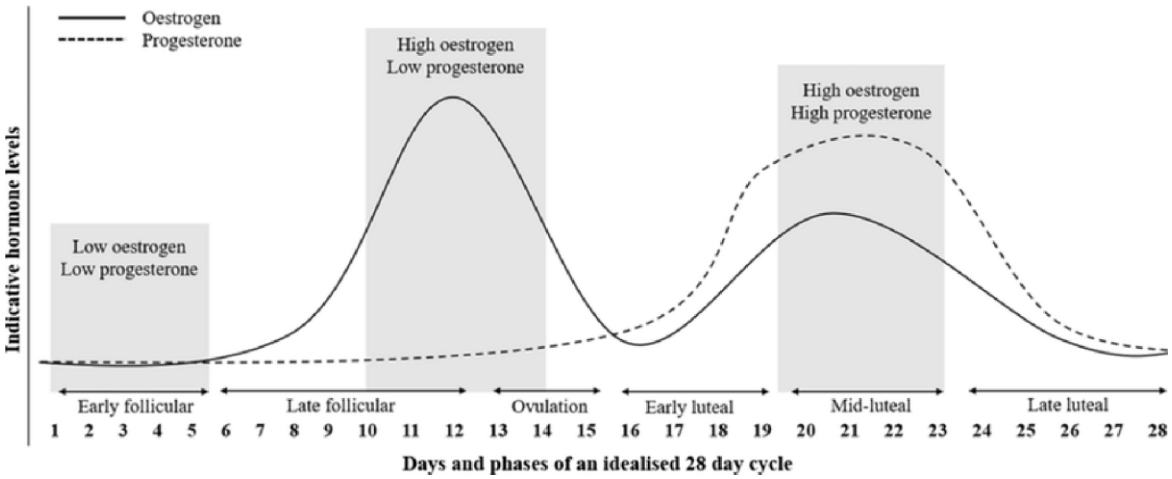

Figure 2: Hormonal fluctuations during a regular 28-day cycle. Showing low estrogen and progesterone levels during the early follicular stage, with estrogen increasing during the late follicular and mid-luteal stage slowly decreasing between ovulation and late luteal stages. Whereas progesterone is low until the early luteal stage where it rapidly increases until the mid-luteal stage. Adapted from McNulty et al., 2020.

Women with endometriosis have cellular and molecular differences in endometrium, compared to controls (Klemmt and Starzinski-Powitz, 2018). A regular menstrual cycle consists of maturation and ovulation of a single oocyte, and thickening of uterine lining, which is then shed in the absence of fertilisation (Agustin et al., 2022). Most stages of menstrual cycle for women with endometriosis follow the normal cycle, i.e. endometrial tissue thickens in preparation for embryo implantation inside the uterus but in individuals with endometriosis the endometrial tissue on organ(s) with endometrial implants also thickens (Arafah et al., 2021). In the absence of implantation, endometrial tissue separates, and sheds, but is unable to exit the body from organs within the pelvic area, leading to its entrapment. This resulting build-up of tissue disrupts the signalling of progesterone and estrogen (Kobayashi et al., 2021). Hormone imbalances caused by the disruption of uterine epithelial growth and proliferation of epithelial cells results in progesterone resistance and estrogen dominance (Fukui et al., 2019).

Endometriosis leads to inflammatory changes in the pelvis through creating a microenvironment rich in hormones, pro-angiogenic and extremely inflammatory within the endometrium (Boucher et al., 2022). This hostility to a developing embryo can affect its viability. A combination of progesterone resistance, poor oocyte/embryo quality, and inadequate expression of endometrial molecules causes hostility to the embryo environment, impeding implantation, or leading to a biochemical pregnancy (Boucher et al., 2022).

Endometriosis may lead to infertility, through the abovementioned factors, and the presence of oxidative damage, and tubo-ovarian anatomy distortion. Statistics show that 50% of infertile women have been diagnosed with endometriosis, and 25% of patients with endometriosis are infertile (Tamura et al., 2019).

1.2 Symptoms of endometriosis

Symptoms of endometriosis are dependent on where endometrial tissue is ectopically situated (Vinatier et al., 2000). Endometrial tissue implanted on the bowel can cause diarrhoea, constipation, pain before, during and after bowel movement and bleeding from the bowel (haematochezia) (Keckstein and Hudelist, 2021). However, these symptoms may also be associated with other conditions such as irritable bowel syndrome (IBS), Crohn's and ulcerative colitis (DiVasta et al., 2021). Endometriosis scar tissue located within the bladder may obstruct the urethra leading to pain before, during and after passing urine, and blood within the urine (Charatsi et al., 2018). These are similar to symptoms of kidney stones and urinary tract infections, making diagnosing endometriosis more difficult (De Resende et al., 2018).

Some symptoms of endometriosis are generalised including pain in the pelvis, groin, legs and back, before, during and after periods, during or after intercourse, pain during internal examinations and headaches (Shi et al., 2022). Severe menstrual cramps cause pain induced vomiting, with sudden bloating also being reported in relation to endometriosis (Dunphy et al., 2022). Endometriosis patients may also experience heavy prolonged bleeding during menstruation, pre-menstrual spotting, irregular periods, with dark blood before and after periods and blood clots (Irshad et al., 2022).

In extremely severe and rare cases of endometriosis pneumothorax and haemothorax may occur (Nezhat et al., 2019). Haemothorax is caused by endometriotic implants in the diaphragm, lungs and pleura displaying as catamenial pneumothorax (Dong et al., 2021). This causes fluid and air to travel into pleural spaces via small openings within the diaphragm (Marjański et al., 2016).

Studies carried out by Voldarsky-Perel et al., (2022) showed women with endometriosis have adverse histopathology and perinatal outcomes following in vitro fertilisation (IVF). Endometriosis-related abnormal perinatal and/or delivery outcomes came from increased fibrin deposition within the intervillous space of the placenta, placenta previa and foetal vascular malperfusion (Voldarsky-Perel et al., 2022). These endometriosis-related placenta abnormalities may occur through chronic inflammation, resistance to increasing progesterone, increased secretion of interleukins and alteration of uterine contractility (Pirtea et al., 2021). Studies by Voldarsky-Perel show the potentially devastating outcomes of endometriosis, highlighting the importance of further research into the causation and treatment of endometriosis.

1.3 Diagnosis of endometriosis

Diagnosing endometriosis is difficult due to high numbers of associated comorbidities, many of which have similar symptoms (section 1.2). Peters et al., (2022) indicated endometriosis has a high occurrence of coexisting gynaecologic conditions including uterine leiomyomas, several different cancers, and gastrointestinal issues. Meaning it can take up to ten years for endometriosis to be identified due to misdiagnosing as one of the coexisting conditions with similar symptomatology (Amro et al., 2022)

There are six different steps to diagnosing endometriosis (Nguyen et al., 2021) (see table 2).

Table 2: Steps used to diagnose endometriosis

Step	**Method of diagnosis**
1	Identify related symptoms (see section 1.2) and investigate for a family history

	of endometriosis. If close family members have the condition, the patient is ten times more likely to develop it potentially due to heritability factors such as genetic variations (this is further explained within section 1.7) (Wessels et al., 2021). Furthermore, IBS, celiac and other coexisting conditions, especially gynaecologic diseases such as polycystic ovaries, pelvic inflammatory disease (PID) and endometrial polyps within a patient's family history are investigated (Hewitt, 2020).
2	An internal pelvic examination follows to identify possible tenderness and pain caused by cysts and scarring around reproductive organs and within the uterus (Wojcik et al., 2022), and other abdominal abnormalities (distention, incisions, and hernias) (Mansfield et al., 2022).
3	An ultrasound scan both trans-vaginally and trans-abdominally is used to identify any large areas of scar tissue and cysts. However, an ultrasound scan cannot detect superficial endometrial cell implantation (endometrial spots). Despite its inability to identify endometriosis stages 1 and 2, an ultrasound is commonly used within early condition stages. Such women will frequently be misdiagnosed as not

	having endometriosis, resulting to their dismissal, and prolonging the time of diagnosis (Chen-Dixon et al., 2022).
4	A magnetic resonance imaging (MRI) scan can be used to map endometriosis, but this is not a common practice (Indrielle-Kelly et al., 2020).
5	The most reliable way to confirm the presence of endometriosis is through a laparoscopy (Mak et al., 2022), this surgical instrument uses fibre-optics to inspect the abdomen and view surrounding tissues. If endometriosis-related scar tissue is found, it can be removed through burning or cutting, depending on size (Goncalves et al., 2021). This is a last option for diagnosing endometriosis due to complications, including infections, scaring, damage to organs, bleeding, and general anaesthesia-associated risks (Nicolaus et al., 2020).
6	Once a definitive diagnosis of endometriosis is made, the patient will be classified with one of the four stages of endometriosis, and appropriate management and treatment strategies will be discussed (Mier-Cabera et al., 2022).

Furthermore, the European society of human reproduction and embryology (ESHRE) guidelines (table 3) states endometriosis is not diagnosed through biomarkers and current imaging techniques do not show superficial or early stages of endometriosis, possibly preventing early-stage diagnosis (Becker et al., 2022).

Table 3: ESHRE (2022) ESHRE guidelines used by clinicians as a guide to diagnose endometriosis using suggestions for clinical examination and diagnostic tests.

ESHRE recommendation	**Strong or weak recommendation**	**Disadvantages to recommendation**
Vaginal examination identifying endometriomas and deep nodules.	Strong	Low diagnostic accuracy.
Biomarkers should not be used.	Strong	No stated disadvantages.
Imaging of ultrasound and MRI.	Strong	Imaging is unlikely to find superficial endometrial implants.
Laparoscopy	Strong	Negative histology is unable to rule out endometriosis.
Follow up support and monitoring.	Weak	Long-term monitoring of endometriosis does not have evidence of benefiting patients in reoccurrence detections, malignancy, or endometriosis complications.

1.4 Treatment and management of endometriosis

There is currently no cure for endometriosis. However, it can be managed and controlled through various strategies dependent on stage, symptoms, and patient lifestyle (Kalaitzopoulos et al., 2021). Combinations of pain medication, hormone therapy and surgery can manage symptoms, regardless of the stage. Despite this, O'Hara et al., (2022) found persistent symptoms in 82.7% of patients having chronic pain with dyspareunia (61.1%) and dysmenorrhea (65.8%). Pain medication mainly consists of non-steroidal anti-inflammatory drugs which reduce inflammation and ease cramps (Vercellini et al., 2018). In severe cases, stronger medications, normally opioids are utilised, but are prescribed with caution due to addictive properties, tolerance, and adverse side-effects (Dinsdale et al., 2021).

Hormone therapy allows management of endometrial pain and inhibits new implants of endometrial tissue, by slowing tissue growth through controlling hormone production. This prevents fluctuation of hormones linked to the breakdown, thickness, and implantation of endometrial tissue (Jensen et al., 2018). Although Mira et al., (2020) found that hormonal treatments can relive symptoms in between 50-80% of cases, in DIE patients 20% of cases had continued symptoms.

The two most common forms of hormonal therapy used are hormonal contraception and progestin therapy (Vannuccini et al., 2022). Hormonal contraception reduces pain and leads to lighter and shorter menstrual flow, by controlling the levels of estrogen (Grandi et al., 2019). Progestin therapy works through ceasing menstrual periods and implant growth of endometrium inside and outside the uterus (Rafique and Decherney, 2017). Additionally, aromatase inhibitors and Gonadotropin-releasing hormone (Gn-RH) agonists/antagonists can also be used to manage symptoms (Carlyle et al., 2020).

Conservative surgery through laparoscopy to remove or burn endometrial implants and tissues can be used in patients with severe endometriosis while preserving the uterus and ovaries which is mainly used in patients who are struggling to conceive (Koninchx et al., 2020). However, 2 years after surgery Ngernprom et al., (2023) found a recurrence of endometriosis symptoms and implants in 23.2% of patients. Demir et al., (2022) found that 33.33% of women affected by stage 3-4

endometriosis were able to conceive naturally following conservative surgery after twenty-four months. The same study reported higher success rates (50%) for women affected having IVF in the 24 months after surgery (Demir et al., 2022). This suggests for more severe endometriosis, IVF is more likely to enable conception.

In severe endometriosis, a hysterectomy and oophorectomy are also considered for women who do not wish to conceive (Long et al., 2022). Oophorectomy leads to menopause from lack of oocyte ovulation and associated hormone cycling, leading to potential improvement of symptoms. Furthermore, hysterectomy induces menopause relieving painful uterine cramps and heavy menstrual bleeding (Alio et al., 2019). Risk factors associated with early menopause are cardiovascular diseases, early death, and metabolic conditions. Additionally, there is a possibility of symptoms of endometriosis remaining after the procedure (Zanello et al., 2019), from ovarian remnant syndrome (ORS) and adhesions post-surgery (Rizk et al., 2014). ORS is the lingering ovarian tissue causing potential symptoms of pelvic masses, pelvic pain, painful intercourse, and painful bowel movements and urination (Ucmak et al., 2019). Magitbay and Magrina, (2006) found ORS occurs within 29% of endometriosis patients after an oophorectomy. Adhesions post-surgery occurs through scar tissue forming after two surfaces of the body rejoin being prominent in 60-70% of hysterectomy cases, causing symptoms of bladder dysfunction, painful bowel movements and chronic pain (Briggs and Beran, 2022). Furthermore, Rizk et al., (2014) found 62% of advanced stage endometriosis had higher recurrence rates after a hysterectomy when an oophorectomy was not also performed, with Manobharath et al., (2023) finding 20% of patients needing continuing surgery after 5 years of both operations.

1.5 Pathways found to be associated with endometriosis.

Garcia-Gomez et al., (2020) and Patel et al., (2018) found differentiated inflammatory systems in endometriosis patients potentially leading to chronic inflammation. Estrogen dominant endometriosis increases release and expression of pro-inflammatory factors creating a positive feedback mechanism through increased inflammation, promoting endometriosis progression (Garcia-Gomez et al., 2020). As endometriosis is characterised by chronic inflammation it is plausible inflammatory pathways are involved in onset and progression (Angioni et al., 2020).

Damage to ectopic endometriosis is prevented through immunomodulatory protein secretion of soluble intercellular adhesion molecule 1 (ICAM-1), inhibiting recognition of endometriotic lesions detection. Endometriosis patients show augmented C chemokine production promoting inflammation of ectopic endometriosis lesions in peritoneal fluid, promoting inflammation of endometrial deposit areas through increased lipid peroxidation and oxidants levels (Patel et al., 2018). Hormonal imbalances may change immune cells functions (T-cells, natural killer cells and macrophages) increasing pro-inflammatory mediator levels within endometrium, blood, and peritoneal cavity. These impede apoptotic pathways, increasing adhesion and proliferation of endometriotic cells through promoting neurogenesis and angiogenesis in endometriotic lesions. Lesions increased through hormonal imbalances dysregulate inflammatory responses preventing cell death and promotes adhesion, cell proliferation and invasion (Garcia-Gomez et al., 2020).

Modifications to adaptive and innate immune systems can lead to chronic inflammation of endothelium (Zou et al., 2020), through lower levels of immune check point inhibitors (programmed cell death protein 1 and programmed death ligand *1*) within endometriosis patients (Abramiuk et al., 2022), preventing a prolonged and damaging immune response (Santoso et al., 2020). Miller et al., (2017) found endometriosis patients had dysregulated immune functions, with increased chemokines and cytokines increasing angiogenesis and growth of tissues influencing endometriotic implants. Therefore, genes associated in regulating specific pathways of immune and inflammatory systems play an important role in onset and development of endometriosis.

1.6 Environmental pollutants associated with endometriosis.

Environmental pollutants come in various forms such as carcinogens and endocrine disruptors (Limbu and Dakshanamurthy, 2022), which are introduced into the environment by industrial processes (Muller et al., 2020). These have an adverse impact on an individual's overall health, specifically the inflammatory pathway (Yen et al., 2019).

Endocrine disrupting chemicals (EDCs) are manmade substances, having the capacity of altering functions of the endocrine system directly altering the action of

hormones (Schug et al., 2013). EDCs can bind onto hormone receptors mimicking their effects, preventing the normal hormone from binding. This interference results in harmful consequences on health such as damage of the reproductive system and possibly leading to endometriosis onset and progression (La Merrill et al., 2020). EDCs are found in everyday products, e.g., cosmetics, food and beverage packaging, toys, and pesticides. Contact may occur through air, diet, skin, or water. Unfortunately, EDCs cannot be completely avoided or removed from use (Schug et al., 2013).

1.7 Genetic aspects of endometriosis

An individual's genetic make-up plays an important role in both their general health, and their risk disease onset during their lifetime. Over 2000 DNA mutations have been described to affect the cystic fibrosis transmembrane conductance regulator gene, leading to cystic fibrosis (Veit et al., 2016). These DNA mutations are recessive, with both parents being carriers to have an affected child. Other conditions, such as strokes, heart attacks, or dementia have a genetic component, but the risk of developing them is multifactorial. Therefore, factors such as environment, nutrition and socioeconomic conditions are also involved in determining disease development.

Endometriosis is likely to be a multifactorial condition, because endometriosis affects women of the same family. A daughter is at higher risk of developing the condition if her mother or sister have the condition. Investigations carried out using twins shows heritability of endometriosis ranges between 47-51% (Treloar et al., 1999; Lee et al., 2013; Saha et al., 2015), suggesting certain families may have one or more predisposing genetic factors to developing endometriosis. The same twin studies suggested 26% of this heritability is from the presence of gene variants, with Saha et al., (2015) finding a 47% genetic correlation for endometriosis predisposition, with the remaining 53% speculated as environmental factors.

A small number of genome wide association studies have been performed leading to the identification of 42 single nucleotide polymorphisms (SNPs) in endometriosis patients (Sapkota et al., 2017; Zondervan et al., 2018; Rahmioglu et al., 2023). Among these identified variants, some have been shown to be implicated in pain

perception/maintenance (signal recognition particle 14 (*SRP14)*, Bcl-2-modifying factor *(BMF)*, Ganglioside Induced Differentiation Associated Protein 1 *(GDAP1)*, Mix-lineage leukaemia translocated to 10 (*MLLT10)*, Bassoon Presynaptic Cytomatrix Protein *(BSN)* and nerve growth factor *(NGF)*) (Rahmioglu et al., 2023). These variants described were mostly associated with more advanced endometriosis stages 3 and 4. To date no variants have been determined to be associated with earlier and less detrimental stages. The identification of such variants is critical because they could enable a more accurate risk assessment and/or diagnose the condition at earlier stages, leading to improved clinical management, and potential prevention of co-morbidities such as the development of infertility.

Studies show endometriosis patients have a differential immune and inflammatory system response, compared to unaffected women. Differentiation, growth invasion, immune escape, and angiogenesis of endometriotic lesions all occur through the action of anti-inflammatory cytokines, causing modifications to the adaptive and innate immune systems (Zhou et al., 2019), leading to chronic inflammation of endothelium (Zou et al., 2020). Negishi et al., (2021) found a potential bacterial trigger for the action of anti-inflammatory cytokines in endometriosis patients through oxidative stress and sterile inflammation occurring from non-specific bacterial infections. Furthermore, Kobayashi et al., (2014) found sterile inflammation through infection may be associated with developing endometriosis. Specifically, upper genital tract microbial infections can initiate chronic inflammation. *Escherichia coli* in this study was found to alter regulation of endometrial defence in women who are genetically susceptible and break the endometrial barrier, potentially promoting growth of endometrial tissue from retrograde menstruation (Kobayashi et al., 2014). It is, therefore, plausible that genes associated in regulating specific pathways of immune and inflammatory systems play an important role in endometriosis onset and development.

Detailed proteomic analysis of plasma taken from younger (average age 18 years) endometriosis patients vs. a control group was performed by Sassamoto et al., (2022). This showed increased activation and enrichment in 63 different proteins related to cell migration and angiogenesis pathways in endometriosis patients, compared to controls. Relationships between proteins and their pathways and the

colours of endometriotic lesions was also found. Specifically, immune cell migration/activation and inflammation pathway upregulation was associated with vascularised lesions. Conversely, downregulation of the same pathways was linked to more severe blue/black and brown lesions.

The literature search undertaken found a wide variety of possible gene variants potentially associated with endometriosis onset and progression. Many papers were either focused on the relationship of endometriosis and comorbidities such as migraines (Adewuyi et al., 2020), infertility (Blasco et al., 2020), and persistence of endometriosis (Cao et al., 2020) rather than the onset of the condition, a topic which continues to remain unclear. The research data currently available, indicates endometriosis is hormone dependent, having a possible genetic predisposition towards development in certain families. It should be noted that the contribution of specific gene variants to the risk of developing this disease and how potential genetic predisposition interacts with modern environmental pollutants is still not well defined. Moreover, studies have mainly focused on women with advanced stages of endometriosis. Therefore, there is limited genetic data available associated with the earlier and less severe stages. Although, the more advanced stages of endometriosis are more severe and can lead to DIE which can cause organs locking into place, the less severe stages of endometriosis can still cause chronic pain and infertility (Macer and Taylor 2012), and therefore, should be investigated. It is plausible that the less severe stages may be caused by environmental factors or genetic variants. Due to some women suffering with endometriosis not developing more severe stages of endometriosis or having a longer time period between each of the stages compared to other women (Cramer and Missmer 2002; Sinaii et al., 2008). By better defining gene variants related to these earlier stages, a more accurate establishment of risk and a timely diagnosis of the condition may be possible. These could enable the prevention of co-morbidities, such as infertility or ovarian cancer and an improved clinical management. A more detailed understanding of pathways associated with endometriosis onset and progression may lead to a better definition of associated aetiology and pathophysiology and improvements in approaches related to management and treatment.

The way that the environment interacts with genetic susceptibility towards development of endometriosis is also unclear. Literature shows many possible environmental factors that can increase endometriosis risk factors such as EDCs (Kim and Kim, 2020). However, there is limited research on genetic susceptibility and how the environment interacts with this. An insight in such interactions is essential for a better management of endometriosis. A more detailed understanding of how the environment interacts with genetic susceptibility could enable a better understanding of how factors within the environment directly affect pathways associated with endometriosis in genetically susceptible patients.

1.8 Genomics England database

Genomics England (GE) was founded in 2013 by the Department of Health and Social care partnering with the National Health Service (NHS) genomic medicine service and the National institute of Health Research to sequence recruited NHS patients 100,000 whole genomes to understand how health and disease is influenced by genes (Genomics England, 2022) (The National Genomic Research Library v5.1, Genomics England. https://doi.org/10.6084/m9.figshare.4530893.v7). Within this database there are over 100,000 genomes sequenced and over 85,000 patients involved. The aim of this database is to enhance research in healthcare (Genomics England, 2022). Bournemouth University and the Department of Life and Environmental Sciences is part of the Genomics England Research Network (GERN) and has been granted access to the GE Research Environment (https://www.genomicsengland.co.uk/initiatives/100000-genomes-project). This is a secure workspace which contains anonymised datasets in the National Genomics Research Library enabling researchers to carry out investigations related to genetic aspects of known diseases and better determine genetic causes of unknown or rare diseases. The 100,000 genomes database has multiple branches separating the data into different categories, e.g., ovarian, and endometrial cancer, testicular cancer, immune disorders, endocrine disorders, metabolism disorders. The aim of GE 100,000 genome project is to use the scientific findings to accelerated translation into patient care.

This database has completed genomic sequences of patients with known diseases or disorders (Genomics England, 2022). This enables researchers to investigate

genomic sequences and variants of genes and their potential impacts on known and rare diseases.

1.9 Aim and objectives.

The aim of this project was to carry out a detailed investigation of genetic factors and their interactions with the environment (e.g. EDCs) which potentially predispose an individual to endometriosis development.

The project has the following 3 objectives:

1. To identify variants capable of predicting endometriosis development.
2. To investigate the way that environmental factors influence the identified genes and their variants and identify intersecting pathways involved in endometriosis development.
3. To predict the possibility of identified variants acting as novel therapeutic targets.

2.0 Methodology

To fulfil the objectives, set out in this study (section 1.9) a workflow of methods was created (see figure 3). Ethical approval needed to be obtained before using participants data within the GE database. Literature reviews were used selecting environmental impacts and genes relevant to endometriosis development and progression. After this the appropriate participants were selected (see criteria in section 2.4) to build a cohort to search for regulatory sequences of variants found in the genes selected.

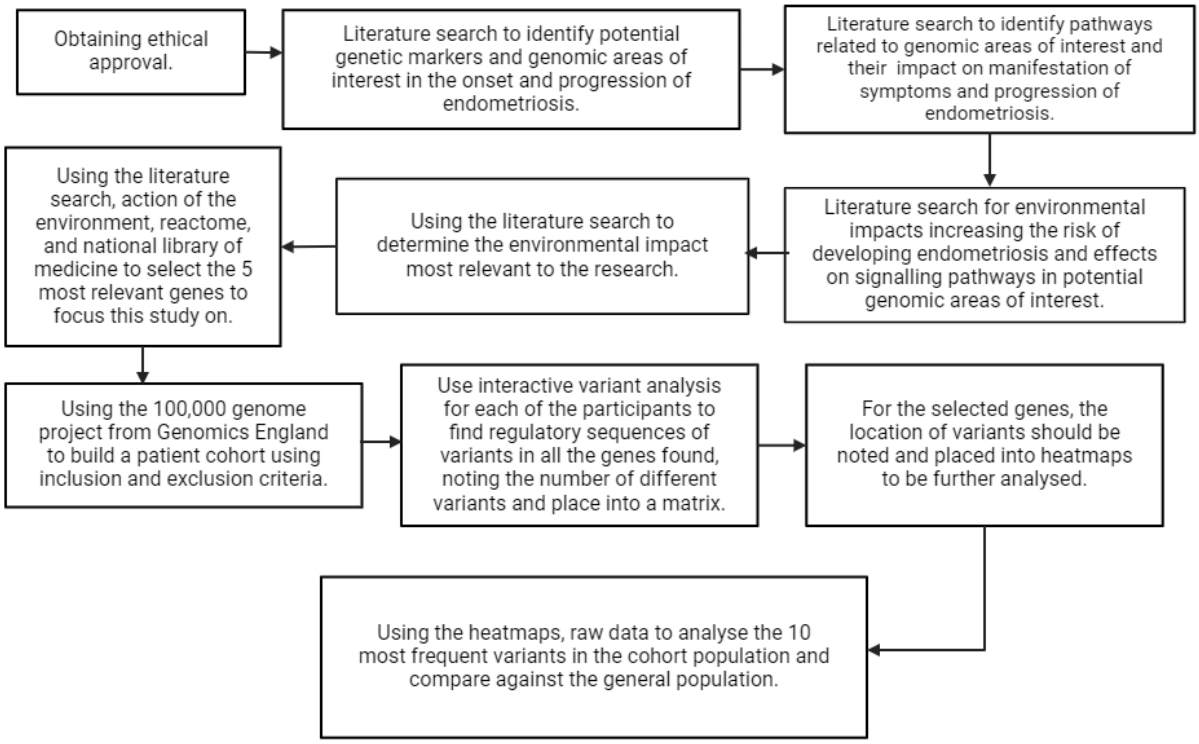

Figure 3: Workflow of methods followed for addressing the objectives set within this study.

2.1 Ethical Approval

The study received ethical approval by the Bournemouth University institutional ethical approval panel, ethics ID: 45978.

2.2 Literature searches

A comprehensive literature search was conducted reviewing current knowledge and identifying potential genetic markers and genomic areas of interest related to endometriosis development under the possible influence of environmental insults.

For the literature review relevant papers published within the last five years were extracted using Web of Science (WOS) and PubMed using the following key words: “endometriosis and “polymorphism” or “SNP” or “genetic polymorphism” or “variants” or “locus” and “GWA” or “Genome-wide” or “Genome wide” or “Genetic association study”. A PRISMA flow chart was created to screen the literature before reviewing current literature on genomic areas of interest related to endometriosis development (figure 4).

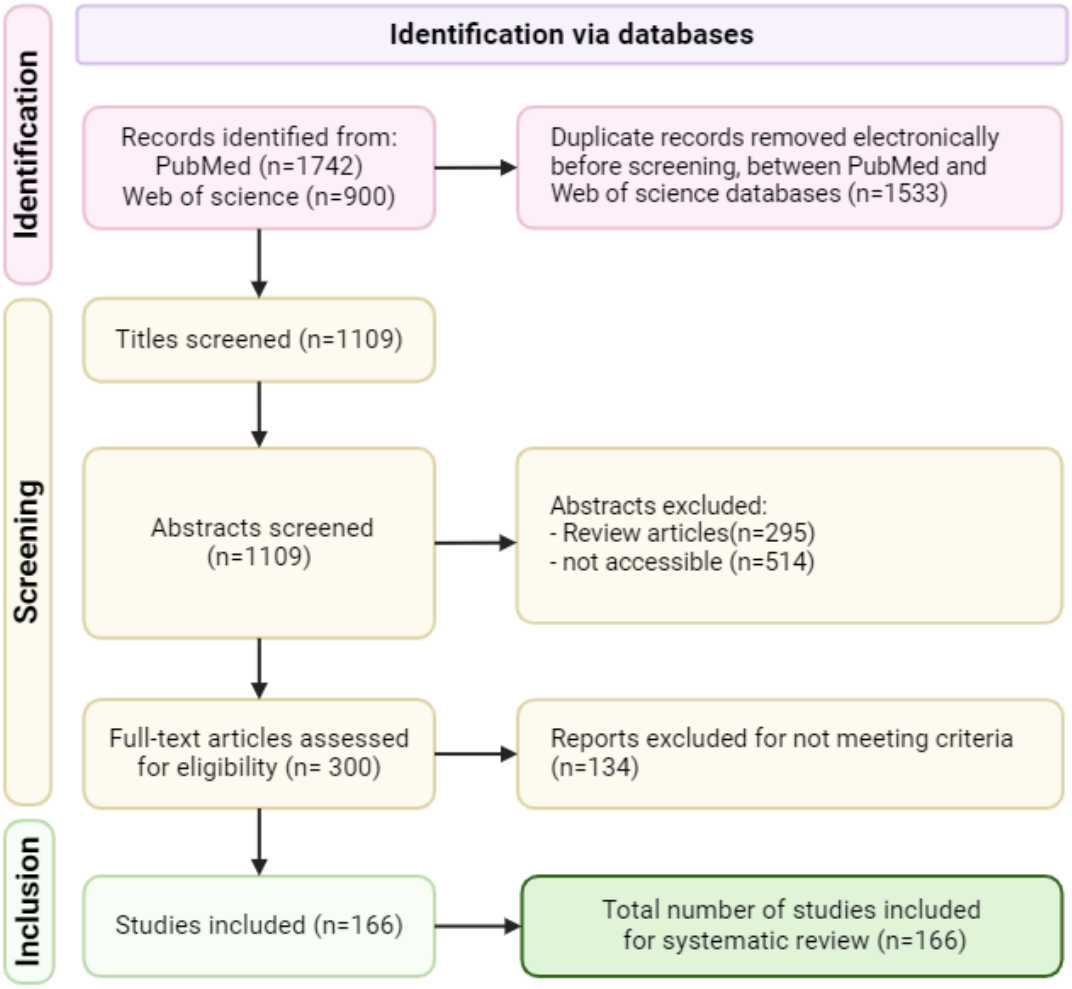

Figure 4: The PRISMA flow chart used to select literature for the genomic areas of interest related to endometriosis development.

The search yielded 166 papers. These were reviewed, and relevant parts were recorded within an Excel spreadsheet enabling easy and accurate conclusions on specific genetic markers, pathways, and genomic areas of interest to the study. To select relevant papers inclusion and exclusion criteria were applied. The inclusion criteria included: original study, study design used (focus on genomic/genetic analysis, or genome wide association design), only human participants (no other species), patients with a diagnosis of endometriosis for at least a year and patients aged between 18-43 years. Exclusion criteria were review studies, studies including patients with other types of female infertility, and without endometriosis diagnosis, and studies with participants over the age of 43 and/or patients with additional illnesses and diseases which could affect the outcome of the results. This yielded 2476 papers to be excluded.

A secondary literature review took place investigating the impact of the environment in increasing the risk of developing endometriosis, and its effects on signalling pathways, which may affect genes within these pathways.

For this literature search original papers published within the last five years were identified only including human participants with a diagnosis of endometriosis using WOS and PubMed. The key words in the search were; “endometriosis and “exposure to endocrine disrupting chemicals”, “endocrine disrupting chemicals”, “exposure to pesticides”, “pesticides”, “personal care products”, “cosmetics”, “exposure to heavy metals”, “heavy metals”, “exposure to radiation”, “radiation”, “exposure to toxins”, “toxins”, “chemicals”, “plastics”, “exposure to pollution”, “pollution”, “exposure to air pollution”, “air pollution”, “exposure to water pollution”, “water pollution”). A PRISMA flow chart was created to screen the literature before reviewing the environmental based literature, this can be seen in figure 5. In total 64 papers were reviewed, and relevant parts recorded within an Excel spreadsheet to enable comparisons across environmental pollutants that could influence the risk of endometriosis development, especially in the presence of variants leading to genetic susceptibility.

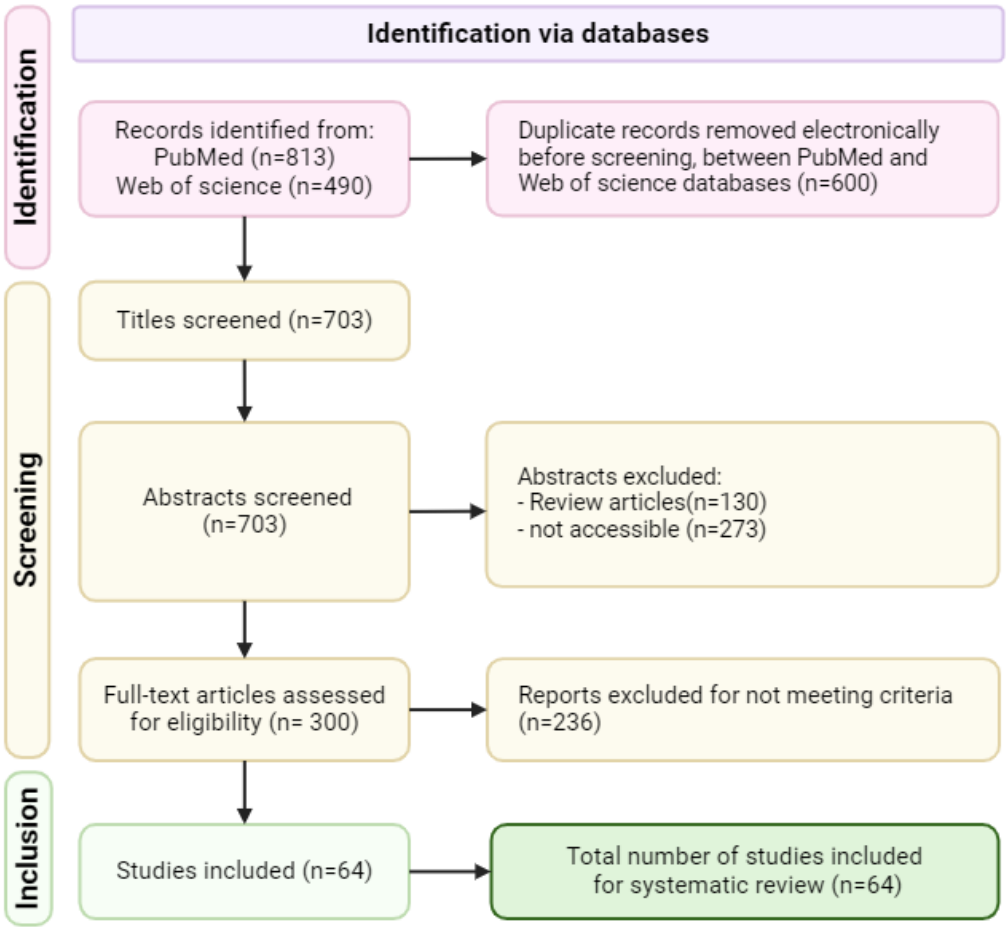

Figure 5: The PRISMA flow chart used to select literature for the impact of the environment on endometriosis risk.

Once the preliminary literature search on the abovementioned areas was complete, the one determined to be most relevant to the current investigation was EDCs. Subsequently, the four most commonly occurring EDCs were examined in greater detail. Areas explored included their structure, properties, uses, signalling pathways affected, mechanisms and association with a genetic susceptibility to endometriosis.

2.3 Selection of genes and their variants

The literature search of genomic markers and genomic areas of interest leading to a susceptibility to endometriosis risk identified a total of 57 genes. From these 57 genes, five were selected to be investigated further. These were *IDO1(*Indoleamine 2,3-dioxygenase 1), *IL-6 (*Interleukin 6), *CNR1 (*cannabinoid receptor 1), *TACR3* (tachykinin receptor 3) and *KISS1R (KISS1* receptor). The decision to focus on these five genes was taken because they were observed to be affected by the action of EDCs in published studies. The criteria for selecting these genes can be seen in table 4.

Table 4: A criteria table for selecting the five genes to be investigated further.

Criteria of selected gene	**Example**	**Rationale**
Literature has shown EDCs are associated with disruption to the gene, this could be altered expression or epigenetic alterations such as cytosine demethylation and modification of histones (Alavian-Ghavanini, and Rüegg, 2018).	The ECD TCDD (2,3,7,8-Tetrachlorodibenzodioxin) upregulates the *IDO1* gene causing an increased state of chronic inflammation (Matta et al., 2021).	This enables an investigation into the influences environmental factors have on endometriosis.
Literature has shown EDCs effects are shown within the signalling pathways the selected genes are involved in. Leading to an alteration to the pathway and disrupting the	DEHP (Di-(2-ethylhexyl) phthalate) exposure influences regulators of HPGA (hypothalamic-pituitary-gonadal axis) by regulating GnRH (Gonadotropin hormone-releasing hormone)	Knowing pathways effected by both genes associated with endometriosis development and ECDs, can enable a better understanding of how the environment and genetic

homeostasis (Lauretta et al., 2019).	release. This disrupts the homeostasis of the HPGA causing a positive feedback mechanism of pituitary release and in turn increasing *KISS1R* expression levels (Graceli et al., 2020).	factors influence endometriosis development and onset.
The pathways associated with the gene are seen to be associated or involved in endometriosis onset or progression.	Due to endometriosis being characterised by chronic inflammation (Angioni et al., 2020), genes involved in the inflammatory pathways such as *IL-6* were considered.	This can identify genes and intersecting pathways involved in endometriosis development.
The selected genes are expressed within tissues associated with endometriosis implant locations.	When women with endometriosis were compared to healthy individuals research showed cellular and molecular differences in their endometrium (Klemmt and Starzinski-Powitz, 2018). Therefore, genes expressed in the endometrium were considered.	Dysregulation of tissue-specific arrangements within genes can lead to diseases within tissues (Aguet and Ardlie, 2016). Dysregulation of genes found within tissues of areas associated with endometriosis implants may be a causative factor for endometriosis development.
The main function of the gene, when disrupted	*IDO1* may influence chronic inflammatory sites	This may show a functional analysis of

potentially leads to development of endometriosis.	through promoting immune dysfunction within the *IDO1*-Kynurenine-Aryl hydrocarbon receptor (*IDO1-KYN-AhR)* signalling pathway.	variants in selected genes found. By understanding the main function of the genes, a hypothesis of variants effect on endometriosis development can be achieved.

Furthermore, the national library of medicine (NIH) (https://www.nlm.nih.gov/) was used in gene selection through identifying the genes full name, where the gene is expressed and the main functions of the gene. Reactome was used to identify potential pathways selected variants were present in and analyse their expression (Gillespie et al., 2022).

2.4 100,000 Genomes Project Database searches

To investigate genetic factors related to endometriosis and their interactions sequencing data stored and publicly available in a biomedical database were searched. The biomedical database used within this study was the 100,000-genome project from GE (as seen in section 1.8). The current research project was part of an approved ongoing larger project in the GE database with the title “Genomic and chromosomal instability sequence markers in relation to fertility, early pregnancy and cancers of the reproductive tissues” Project ID 645. The included Domains were as follows:

- Ovarian cancer GERN domain
- Endocrine and Metabolism GERN domain

Data was extracted from the GE participant explorer (PE) through searching clinical diagnosis according to specific inclusion and exclusion criteria. A preliminary examination of the database was focused on the patient cohorts with endometriosis

stated in clinical notes available with the inclusion and exclusion criteria shown in table 5.

Table 5: Inclusion and exclusion criteria to identify participants with data relevant to the study.

Inclusion criteria	**Exclusion criteria**
Females aged 18-43 years	Females aged older than 43 years
Endometriosis	Diabetes
Endometriosis-related infertility	Additional ovarian pathology
Endometriosis-related ovarian chocolate cysts	Chromosomal/ genetic abnormalities
	Haematological/ immunological disorders
	Other hormonal disorders
	Underweight (body mass index below 18.5) or obese (body mass index over 30)
	Uterine abnormalities

Participants with endometrial cancer were grouped separately before interrogation of the data. It should be noted that the stage of endometriosis was not stated in the PE database. Therefore, endometriosis stages were estimated using additional clinical information available, e.g., the type(s) of endometriosis implants and procedures conducted in relation to the condition and from the information given in table 1 and figure 1, with table 6 showing the criteria used in this study to estimate the patient's endometriosis stage.

Table 6: criteria used in this study to estimate the patient's endometriosis stage.

Stage	**Clinical information to diagnose endometriosis stage**
Stage 1	Minimal surgeries such as examination of uterus and laparoscopic approach to abdomen, with 1 or 2 locations of endometriosis within the ovary, pelvic peritoneum, uterus or rectovaginal septum and vagina.
Stage 2	Had two or more locations of endometriosis within the ovary, pelvic peritoneum, uterus or rectovaginal septum and vagina and minimal surgeries such as examination of uterus and laparoscopic approach to abdomen, including removal of lesions.
Stage 3	Multiple locations of endometriosis, chocolate cysts and multiple surgeries including cauterisation of organs, endoscopic freeing of adhesions and extirpation of ovaries.
Stage 4	All locations of endometriosis including possible endometriosis located in the intestine in some cases, chocolate cysts and procedures of endoscopic resection, endoscopic destructions, repair of obstetric lacerations, drainage of ovarian cysts and endoscopic extirpation.

This created 4 patient cohorts. The sample size of each cohort was determined by data availability for each group (sample sizes within the cohorts were comparable) with details provided in section 2.5.

Genes and variants related to risk of endometriosis development were determined using interactive variant analysis (IVA) tool located within the GE database. IVA is a variant browser enabling a search into variants found within GE participants through selecting for genes, frequency and consequences by family genotypes and patient IDs. Once patients matching the inclusion criteria were identified, a search using IVA for each of the 57 genes of interest, their regulatory sequences of single nucleotide variations (SNVs) and insertion-deletion mutations (INDEL's) followed. The number of variants/mutations was noted for each of the 57 genes. The location of variations/mutations was noted for the 5 genes found from the literature search. Regulatory sequences were investigated rather than coding sequences due to the current GE database only recording introns within the participant cohort and not exons. Furthermore, environmental pollutants are most likely to act upon regulation of genes, therefore, investigating regulatory sequence variants and their impact on gene expression can help to investigate environmental pollutants effect on gene expression in relation to endometriosis.

2.5 Gene variant data analysis

Within GE a specific new database was created for the patient group with a defined structure. To protect patient identity small numbers and percentages were documented as <5 or <35% and had to pass through an airlock for approval.

This included:

a. Specific clinical data fields and clinical results
b. Clinical conditions associated with the selected patients.
c. Anonymised patient characteristics
   Anonymised patient IDs with links to the whole genome data related to polymorphic markers.

2.6 Potential biases in the data from this study

This study has several potential biases involved in the data obtained, this is shown in table 7.

Table 7: Potential biases in the data from this study

Bias	**Impact**
Small sample size	The possibility of chance findings is increased in small sample sizes and can challenge the validity of the study produced.
Cohort is not diverse in ethnicity (mainly White British).	When different ethnicities are not represented meaning genomic ancestry and genetic association is not accounted for, to account for varying ethnicities. This underrepresentation potentially prevents biomarkers from being accessible to ethnicities other than white.
Phenotypic misclassification	Misclassification of phenotypes can cause either diluted or inflated effect sizes.
Misdiagnoses of stage	Due to stages not being stated in GE, stages had to be estimated using set criteria. This potentially leads to misdiagnosis of a patient's stage, leading to variants found potentially not being relevant to specific stages.
Overrepresentation of western educated, industrialised, rich and democratic societies in the GE database (Genomics England, 2022).	Genomics England, (2022) has described overrepresentation of these societies does not benefit genomic medicine, specifically in this study the

	overrepresentation of these societies does not allow for biomarkers to be used for all diverse personnel and can lead to distrust.

2.7 Statistical analysis

To analyse 57 genes regulatory sequences a matrix was created within Excel, including each of the participants number of SNVs and INDELS enabling analysis of calculating the average, range, and standard deviation for each gene.

Although 57 patients were found in PE only 19 patients could be found within IVA, therefore, 19 patients were used in finding potential variants. Once data was collected and organised in GraphPad Prism, heatmaps were constructed to visually highlight which variants in the five selected genes were most frequent in endometriosis patients for this cohort. Some heat maps were split into several parts due to genes having a larger number of variants. Through analysing the raw data and heatmaps the ten most frequent variants within the cohort population were selected. The raw data was used to find variants observed in multiple stages and patients, with the heatmaps enabling initial visual observation of variants highlighted more frequently. Variants chosen were then compared with the frequency in GE to observe if these were common in the endometriosis cohort or the general population.

This was subsequently followed with two Chi-squared tests (χ^2). The variant frequencies obtained from the GE database were found through the GE database providing the frequency as a percentage of each variant in the GE total population of all the participants genomes sequenced. This is provided in the IVA platform of GE. Frequency for the variants in the endometriosis cohort was used as the observed frequency and GE total population frequency for each variant was used as the expected frequency. The significant level from the χ^2 was calculated using 1 degree of freedom (df) and a P-value of 0.001, leading to any variants with a χ^2 value of over 10.827 to be significant. As GE was unable to provide the number of participants in the database and the number of participants with the selected variants in the database, the df was determined by the cohort frequency percentage used and the GE frequency percentage used for each variant (2-1) for the df. Another χ^2 test was

performed using counts, where the expected frequency was the expected number of participants in the population to have the variants and the observed frequency was the participants in the cohort population who had the variants. This χ^2 was used using a 1 df, a P-value of 0.05, leading to any variants with a χ^2 value of over 3.841 to be significant. After this a random sample of nineteen participants from GE were selected to account for the small sample size, where a χ^2 Goodness-of-Fit test and a Fisher's combined probability test was conducted for both the endometriosis cohort and the random sample compared to the GE total population. This was followed by a Benjamini-Hochberg (BH) correction to ensure there were no false results and to ensure confidence in the findings. An ANOVA was also conducted to find the statistical significance of the ages of the patients when diagnosed compared to the stage of endometriosis.

2.8 Regulatory sequences analysis

To find the regulatory sequence and the impact of statistically significant variants an extensive search was taken using the reference SNP ID number (rsID) in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/?term=672[geneid], http://www.ncbi.nlm.nih.gov/clinvar/?term=c.1018delG, http://www.ncbi.nlm.nih.gov/clinvar/?term=17[chr]+AND+43000000:44000000[chrpos37]), dbSNP (https://www.ncbi.nlm.nih.gov/snp/ (Sherry et al., 1999), Ensembl ((Ensembl 2023)https://www.ensembl.org/index.html) , String version 12.0 (https://string-db.org/ (Szklarczyk et al., 2023)) and UCSC (http://genome.ucsc.edu Nassar et al. The UCSC Genome Browser database: 2023 update. The workflow for this can be seen in figure 6.

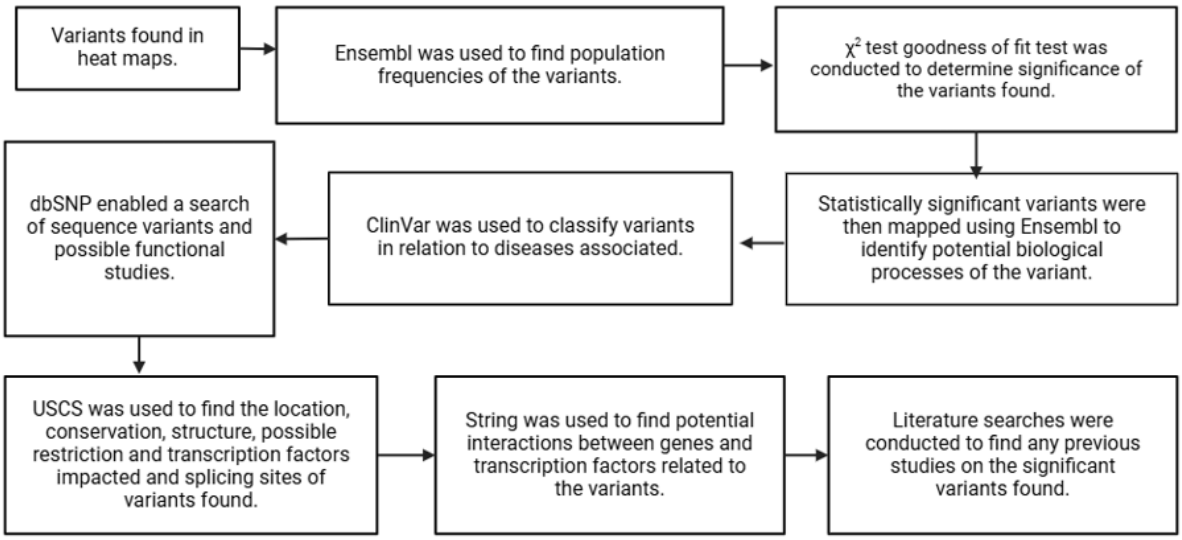

Figure 6: Workflow of methods followed for finding the impact and regulatory sequences of statistically significant variants.

The variant frequencies obtained from Ensembl through searching each variant, and going to Ensembl's population and individual's database, this provided the 1000 genomes project phase 3 allele frequencies in the different populations, such as the whole population and subpopulations such as African, and European. Ensemble was also used for finding the chromosomal locations for each significant gene (Ensemble 2023). ClinVar was used to classify the variants in relation to the disease, this database gives a description if the variant is pathogenic and the functional consequence of the variant. DbSNP was used to find any previous literature on the variants, the frequency of the variant in the general population and subpopulations such as African American, European and Asian. UCSC was used to find the location, conservation structure, transcription factors impacted, and splicing sites of the variants. String was used to find any potential pathways or processes involved in the genes of the variants and transcription factors impacted by the variants. These searches were achieved through searching each of the variants in the databases.

The extensive search of the rsID shown in figure 6 and a literature search for the variant selected can enable an understanding of the regulatory sequence and the

impact of the variant, therefore, aiding in the understanding of how the selected gene may influence the onset and progression of endometriosis.

3.0 Results

3.1 Participant details

Of the 57 patients identified, endometrial tissue was mostly seen (86%) to be present on the ovaries, and least commonly detected (<5) on the intestines, 70% of patients were diagnosed with an unspecified form of endometriosis where the location of endometriosis lesion or implant was not specified within PE.

The main way to diagnose endometriosis for this cohort was through laparoscopy (38%), while <35% underwent cauterisation of endometriotic implants to remove lesions from affected organs.

Of the 57 participants, the youngest were affected by endometriosis stages 3 and 4 (average age 36.3 years and 36.5 years respectively). The oldest were affected by stage 2 endometriosis (average age 39.7 years) seen in table 8.

The average age of diagnosis was 31 years for stages 1 and 2, indicating milder stages of endometriosis took longer to be diagnosed. Severe stages (3 and 4) were identified sooner, with the average ages being 30 and 29 years, respectively. An ANOVA was conducted on the ages of diagnosis per stage, however, the ANOVA showed no statistical significance between the stage of endometriosis and the age of diagnosis.

Table 8: Overview of participants found within GERN and included in this study shows full information of each participant categorised according to age groups of 29 years and lower, 30-36 years and 37 years and higher.

Stage of endometriosis	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**

Number of participants	10/57 (17.5% of cohort population)	19/57 (33.3% of cohort population)	21/57 (37% of cohort population)	7/57 (12.3% of cohort population)
Age range (years)	30-43	28-43	27-43	26-41
Average age (years)	38.5	39.7	36.3	36.5
Average age of initial endometriosis diagnosis (years)	31	28	26	26
Number of different endometriosis locations	5	7	9	10
Most common endometriosis type (%)	Endometriosis of ovary (100%, 10/10)	Endometriosis of ovary (79%, 15/19)	Endometriosis of ovary (81%, 17/21)	Endometriosis of both ovary and pelvic peritoneum (100%, 7/7- ovary, 100%, 7/7- pelvic peritoneum)
Other endometriosis types	Endometriosis of rectovaginal septum and vagina, Endometriosis	Endometriosis of uterus, Endometriosis of pelvic peritoneum.	Endometriosis of fallopian tube, Endometriosis of	Endometriosis of intestine, Endometriosis of fallopian tube,

	of uterus, Endometriosis of pelvic peritoneum.		rectovaginal septum and vagina, Endometriosis of uterus, Endometriosis of pelvic peritoneum.	Endometriosis of rectovaginal septum and vagina, Endometriosis of uterus.

Most (41/57, 72%) participants were classified as white British, with other included ethnicities being Asian and Black African. Due to the limited number of patients with ethnicities other than white British, all non-white British ethnicities were grouped together.

3.2 Variants of the 57 genes in the participant cohort

57 genes were found during the literature search to identify potential genetic markers and genomic areas of interest in relation to endometriosis onset and progression (genes and associated biological processes are summarised in table 9).

Table 9: Genes of interest and associated biological processes, as identified during a literature search for potential genetic markers and genomic areas of interest in relation to endometriosis onset and progression.

Biological process	**Genes involved**
Pain perception/ management	*Catechol-O-methyltransferase (COMT), BMF, BSN, cyclin-dependent kinase inhibitor 2B antisense RNA 1 (CDKN2B-AS1), Kirsten Rat Sarcoma viral oncogene homolog (KRAS), PDZ domain containing ring finger 3*

	(PDZRN3), protein tyrosine phosphatase receptor type D (PTPRD).
Inflammation pathway	*Tumor necrosis factor alpha (TNF-a), interleukin 1 beta (IL1-b), IL-6, interleukin-1 alpha (IL1A), nuclear factor erythroid 2-like 1 (NFE2L1), centrosomal protein 112 (CEP112), malignant fibrous histiocytoma-amplified sequence 1 (MFHAS1), MLLT10, solute carrier family 35 member G6 (SLC35G6).*
Immune pathways	*IDO1, kinase insert domain receptor (KDR), fibronectin 1 (FN1), interferon gamma (IFNG), IL1A, tankyrase (TNKS), TACR3, Tachykinin precursor (TAC), KiSS-1 Metastasis Suppressor (KISS1), KISS1R, SRP14, Src kinase-associated phosphoprotein 1 (SKAP1), Ewing tumor-associated antigen 1 (ETAA1), ADP ribosylation factor like GTPase 14 effector protein (ARL14EP), N-acetyltransferase 2 (NAT2), Rho family GTPase 3 (RND3), SR-related CTD associated factor 11 (SCAF11), transcription factor AP-2 delta, or activating enhancer binding protein 2 delta (TFAP2D), zinc finger protein 536 (ZNF536).*
Related to migration	*Phosphatidylinositol-3 kinase (PI3K), cell division cycle 42 (CDC42), AT-rich interaction domain 1A (ARID1A), KIT*

	ligand (KITLG), SMAD family member 3 (SMAD3), kinesin family member 3A (KIF3A).
Related to angiogenesis	*Mitogen-activated protein kinase (MAPK).*
Sex-hormones/ hormones	*Estrogen receptor 1 (ESR1), follicle stimulating hormone subunit beta (FSHB), KISS1, TACR3, CNR1, growth regulating estrogen receptor binding 1 (GREB1), progesterone receptor gene (PGR), cytochrome P450 family 17 subfamily A member 1 (CYP17A1), neurokinin B receptor (NKB3R).*
Cell differentiation	*Wingless-type MMTV integration site family, member 4 (WNT4), vezatin, adherens junctions transmembrane protein (VEZT), tripartite motif-containing protein 32 (TRIM32), Krüppel-like factor 3 (KLF3), Inhibitor of Differentiation 4 (ID4), NGF, GDAP1.*
Cell adhesion	*LIM domain only protein 7 (LMO7).*
Cell growth	*Murine double minute 2 (MDM2), nuclear factor, erythroid 2-like 3 (NFE2L3).*
Cellular processes	*Poly(ADP-ribose) polymerase family member 11 (PARP11), DNA primase subunit 2 (PRIM2), RAB GTPase activating protein 1 (RABGAP1L),*

	chromobox 1 (CBX1), cytochrome P450 family 2 subfamily C member 19 (CYP2C19), glutathione S-transferase mu 1 (GSTM-1).

Out of 57 genes identified, 19 (33.3%) were related to immune pathways, 9 (16.7%) related to inflammatory pathways, 7 (12.2%) control pain perception and management, 29 (50.8%) were associated with tissues in the ovaries and 34 (60%) with endometrial tissue. The genes and associated tissue of expression can be seen within table 10.

Table 10: Tissues associated with each of the 57 genes with the data collected from the NIH.

Tissue Associated With Gene	**Gene**
Thyroid	*ZNF536, VEZT, ID4, ETAA1, ARL14EP*
Endometrium	*ZNF536, VEZT, TRIM32, SRP14, SKAP1, SCAF11, RND3, RABGAP1L, PRIM2, PGR, PDZRN3, PARP11, NFE2L1, MLLT10, MFHAS1, MDM2, KRAS, KLF3, KITLG, KIF3A, KDR, IL-6, IL1A, IDO1, ID4, GDAP1, ETAA1, ESR1, COMT, CEP112, CDC42, CBX1, BMF, ARL14EP*
Urinary bladder	*SMAD3, RND3, PARP11, KLF3, IL-6, IL1A, IFNG, CBX1, ARL14EP, TACR3*
Lymph nodes	*SKAP1, SCAF11, PRIM2, PARP11, MFHAS1, IL-6, IFNG, IDO1, CNR1, ARL14EP, KISS1R*

Brain	ZNF536, TNKS, RABGAP1L, PTPRD, KRAS, KIF3A, ID4, GDAP1, CNR1, CBX1, BSN, KISS1R, TACR3
Ovary	*WNT4, VEZT, TNKS, SMAD3, SCAF11, RABGAP1L, PTPRD, PRIM2, PGR, PDZRN3, PARP11, NGF, NFE2L1, MLLT10, MFHAS1, MDM2, LMO7, KRAS, KLF3, KIF3A, ID4, GSTM-1, GREB1, GDAP1, ESR1, COMT, CEP112, CDC42, CBX1*
Colon	*NAT2, MFHAS1, MDM2, KRAS, KITLG, CNR1, CDKN2B-AS1, CDC42, TACR3*
Small intestine	*NAT2, CYP2C19, CDKN2B-AS1*
Adrenal	*IL-6, CYP17A1*
Stomach	*CYP2C19*

The number of SNVs and INDEL's for each of the 57 genes influencing the risk of developing endometriosis were investigated, unexpectedly all the genes in table 11 were seen to have more SNV's when compared to INDEL's, as SNVs tend to be more commonly occurring in the genome, whereas INDEL's are rarer (Abel et al., 2013).

Table 11: Using data from all the participants the average number, range and standard deviation was calculated for the SNVs and INDEL variants seen for the 57 genes (in GE) that published studies suggested to have a role in increasing the risk of developing endometriosis.

Gene	Reference from the paper that suggested a role within endometriosis	Average SNV from Genomics England	Range SNV from Genomics England	Standard deviation SNV from Genomics England	Average INDEL from Genomics England	Range INDEL from Genomics England	Standard deviation INDEL from Genomics England
ARL14EP	Adewuyi et al., 2020	27	0-54	12.78	10	1-15	4.03
BMF	Rahmioglu et al., 2023	44	32-59	6.70	8	6-12	1.45
BSN	Rahmioglu et al., 2023	130	26-161	23.38	42	9-51	8.15
CBX1	Mortlock et al., 2022	70	0-113	22.87	25	0-37	7.40
CDC42	Gallagher et al., 2019	92	71-113	13.02	28	21-37	3.68
CDKN2B-AS1	Cardoso et al., 2020	76	8-212	86.91	14	2-37	14.60
CEP112	Papageorgiou et al., 2023	1262	832-1548	237.32	237	167-288	33.02
CNR1	Allam et al., 2022	35	20-58	9.96	4	1-8	1.99
COMT	Zhai et al., 2019	89	48-118	22.35	16	10-21	2.81
CYP17A1	Zubrzycka et al., 2020	20	1-29	10.26	3	0-6	2.19

CYP2C19	Perini et al., 2023	91	39-222	51.93	12	5-29	5.85
ESR1	Gallagher et al., 2019, Zubrzycka et al., 2020	600	352-857	167.47	110	76-147	23.64
ETAA1	Cardoso et al., 2020	31	1-60	13.15	7	2-12	2.96
FN1	Cardoso et al. 2020, Mortlock et al., 2022	114	88-211	35.17	48	39-61	6.82
FSHB	Gallagher et al., 2019	19	1-33	12.26	3	0-6	1.88
GDAP1	Rahmioglu et al., 2023	290	195-398	47.58	62	46-72	6.69
GREB1	Gallagher et al., 2019, Mortlock et al., 2022, Zubrzycka et al., 2020	282	199-397	46.84	77	62.91	9.72
GSTM-1	Mear et al., 2020	49	12-100	19.91	3	0-9	2.79
ID4	Mortlock et al., 2022	19	11-26	4.50	5	3-6	1.33
IDO1	Tanha et al., 2022	54	14-116	29.89	14	5-24	5.42

IFNG	Mear et al., 2020	18	1-26	6.03	8	3-11	1.88
IL1A	Cardoso et al., 2020	30	4-53	15.85	11	1-76	15.00
IL6	Benjamin et al., 2020	23	10-33	5.47	4	1-7	1.65
KDR	Mortlock et al., 2022	80	50-106	15.56	15	8-21	3.34
KIF3A	Li et al., 2021	81	53-124	16.04	14	10-18	2.04
KISS1	Blasco et al., 2020	23	7-43	10.88	6	1-9	2.49
KISS1R	Blasco et al., 2020	44	25-66	10.50	14	6-20	2.88
KITLG	Painter et al., 2018	82	44-153	20.18	21	0-26	5.19
KLF3	Painter et al., 2018	56	41-70	7.77	17	11-24	3.93
KRAS	Li et al., 2021	89	51-134	20.87	24	11-30	4.84
LMO7	Painter et al., 2018	317	239-449	56.45	89	67-101	8.83
MDM2	Li et al., 2021	69	15-123	27.85	25	2-41	9.61
MFHAS1	Adewuyi et al., 2022	280	153-398	74.64	46	30-59	7.26
MLLT10	Rahmioglu et al., 2023,	121	57-272	44.23	55	37-89	10.82

	Adewuyi et al., 2022						
NAT2	Wei et al., 2019	62	30-77	12.50	6	4-9	1.37
NFE2L1	Mortlock et al., 2022	28	10-53	12.87	8	4-13	2.67
NFE2L3	Cardoso et al., 2020	43	11-100	29.35	9	1-22	6.68
NGF	Rahmioglu et al., 2023	89	67-130	16.04	10	0-18	4.75
PARP11	Painter et al., 2018	82	15-209	70.83	16	5-35	10.08
PDZRN3	Painter et al., 2018	391	311-502	44.52	71	59-81	7.26
PGR	Zhang and Wang, 2023	169	106-243	49.65	38	25-48	6.80
PRIM2	Painter et al., 2018	391	272-503	67.22	82	54-97	12.38
PTPRD	Painter et al., 2018	4511	3925-6431	478.61	756	682-998	64.74
RABGAP1L	Adewuyi et al., 2022	627	183-1215	385.65	187	74-334	92.93
RND3	Cardoso et al., 2020	88	35-131	31.35	21	10-29	4.82
SCAF11	Li et al., 2021	50	13-70	13.45	14	3-25	4.18

SKAP1	Adewuyi et al., 2022, Painter et al., 2018	293	85-442	92.21	102	35-133	24.99
SMAD3	Adewuyi et al., 2022	260	194-319	34.41	47	37-56	4.64
SRP14	Rahmioglu et al., 2023	31	18-46	8.87	5	3-8	1.33
TAC3	Blasco et al., 2020	6	2-32	6.15	3	2-4	0.58
TACR3	Blasco et al., 2020	143	50-401	90.45	37	15-85	19.84
TFAP2D	Painter et al., 2018	52	8-88	27.48	19	7-27	6.78
TNKS	Adewuyi et al., 2022	445	300-653	110.96	75	54-94	13.22
TRIM32	Adewuyi et al., 2020	33	16-42	7.04	9	7-12	1.69
VEZT	Cardoso et al., 2020	114	25-209	53.27	36	6-60	14.72
WNT4	Cardoso et al., 2020, Gallagher et al., 2019, Adewuyi et al., 2022	49	39-62	7.02	9	7-12	1.42
ZNF536	Painter et al., 2018	588	402-787	85.37	148	95-177	19.67

3.3 Genomic findings of 5 selected genes in study participants

Using the selection criteria in table 3, five genes were selected to investigate further after the initial literature search, the outcomes can be seen in table 12.

Table 12: A table of the outcomes of the 5 selected genes to be investigated further using the selection criteria.

Criteria	**Gene**	**Outcome**
Criteria 1: literature has shown EDCs are associated with disruption to the gene.	*IDO1*	Merrill et al., (2023) found phenol exposure specifically BPA (Bisphenol A) and TBBPA (Tetrabromobisphenol A) can decrease methylation of *IDO1*'s mRNA and DNA, and Tanha et al., 2022 found *IDO1* expression levels were increased when exposed to TCDD when compared to no exposure.
	IL-6	Exposure to TCDD was found to increase *IL-6* expression levels when exposed to TCDD when compared to no exposure (Tanha et al., 2022).
	CNR1	Forner-Piquer et al., (2018) found exposure to diisononyl phthalate (DiNP) and BPA significantly increased *CNR1* expression.
	KISS1R	DEHP exposure influences regulators of HPGA by regulating GnRH release altering *KISS1R* expression (Xie et al., 2022).
	TACR3	DEHP exposure influences regulators of HPGA by regulating GnRH release altering TAC*R3* expression (Xie et al., 2022).
Criteria 2: literature has shown EDCs effects are	*IDO1*	Liu et al., (2022) found EDC's can lead to a dysregulated inflammatory response.

shown within the signalling pathways the selected genes are involved in.		Specifically, BPA was found to be positively associated with pro-inflammatory markers expression.
	IL-6	The toxicity of BPA enables amplification of estradiol leading to increased oxidative stress and inflammatory signals through increased estrogen sensitivity (Ruiz et al., 2021).
	CNR1	DEHPs ability to upregulate metabolising enzymes related to ECS (endocannabinoid system) such as *CNR1* during adipogenesis causes secretion of leptin, adipokines and adiponectin, causing alteration to adipocytes involvement in endocrine function (Ernst et al., 2020).
	KISS1R	DEHP alters levels of reproductive hormones after exposure, specifically higher levels of *FSHR* (follicle-stimulating hormone receptor) serum and in turn *KISS1R*, through DEHP influencing the positive feedback of the GnRH pathway (Graceli et al., 2020).
	TACR3	DEHP exposure influences regulators of HPGA by regulating GnRH release altering *TACR3* (Xie et al., 2022).
Criteria 3 outcome: pathways associated with the gene are seen to be associated or involved in endometriosis onset or progression.	*IDO1*	*IDO1-KYN-AhR* signalling pathway can promote immunosenescence (immune dysfunction) and suppresses effector immune cell functions. While impairing autophagy, remodels extracellular matrixes and stimulates cellular senescence. This is through *IDO1* catabolising L-tryptophan *(L-Trp)* into nuclear factor kappa B

		(NFK) following into kynurenine (*KYN*) which stimulates the *KYN* pathway (Zhang et al., 2024).
	IL-6	*IL-6* stimulates the expression of scavenger receptor cysteine-rich type 1 (*CD163*) a macrophage receptor specialising in tissue repair, which then releases soluble *CD163* (*SCD163*) which is taken up via T-cells and binds to non-muscle myosin heavy chain type a (*MYH9*) which can inhibit proliferations of T-lymphocytes (Gillespie et al., 2022).
	CNR1	Immune cells and inflammatory factors directly influence inflammation of tissues affected by ECS which CNR1 is involved in, because they change behaviour and production of immune cells (Rahaman and Ganguly, 2021), acquiring qualities of anti-proliferative, anti-nociceptive and anti-inflammatory (Lingegowda et al., 2022).
	KISS1R	Ziarniak et al., (2022) theorises *KISS1R* aids in endocrine regulation, with Moise-Silverman and Silverman, (2022) verifying this theory due to *KISS1R*'s involvement in puberty onset through proportionally releasing GnRH.
	TACR3	*TACR3* serves as a receptor for tachykinins with association in; immune, hormonal, Class A/1 (Rhodopsin-like receptors) and G protein-coupled receptor (GPCR) downstream signalling pathways and is associated with HPGA regulating release of *GnRH* (Casteel and Singh, 2020).

Criteria 4 outcome: selected genes are expressed within tissues associated with endometriosis implant locations.	*IDO1*	*IDO1* has sex-biased expression (sex enriched in females) (Yi et al., 2020) and is specifically expressed within the adipose tissues, adrenal gland, colon, endometrium, oesophagus, fallopian tube, heart, kidney, liver, ovary, rectum, saliva-secreting gland, skeletal muscle tissue, small intestine, smooth muscle tissue, stomach, and thyroid gland (Gillespie et al., 2022).
	IL-6	Expression levels of *IL-6* within the cerebral cortex, colon, duodenum, endometrium, fallopian tubes, heart, liver, lymph nodes, pancreas, placenta, rectum, small intestine, spleen, stomach, urinary bladder, and vermiform appendix (Gillespie et al., 2022).
	CNR1	*CNR1* has sex biased expressed in the adipose tissue, colon, endometrium, oesophagus, fallopian tube, gall bladder, lung, lymph node, ovary, placenta, rectum, saliva-secreting gland, small intestine, smooth muscle tissue, spleen, tonsil, urinary bladder, and vermiform appendix Gillespie et al., 2022).
	KISS1R	High expression within the brain. With low expression within all organs mainly the lymph node, placenta and appendix (Gillespie et al., 2022).
	TACR3	*TACR3* is expressed within the cerebral cortex, kidney, and urinary bladder (Gillespie et al., 2022).
Criteria 5 outcome: main function of the gene, when	*IDO1*	*IDO1* can increase growth of endometriosis implants by implantation and invasion of

disrupted potentially leads to development of endometriosis.		shedding endometrium within peritoneum (Kong et al., 2021), through the enhancement of endometrial stromal cells invasion and survival within signalling pathway c-Jun N-terminal kinase (JNK) activation (Song et al., 2016). Mei et al., 2013 found increased expression of *IDO1* within endometrial stromal cells of endometriosis patients compared to controls. Increased expression may lead to increased survival, apoptosis, invasion, and proliferation of endometrial stromal cells.
	IL-6	*IL-6* function is within inflammation and maturation of B cells pathways, with translated protein secreted into serum at sites of chronic and acute inflammation induction (Aliyu et al., 2022). When *IL-6* is dysregulated production of cytokine secretion in endometrial tissues rises, increasing cellular proliferation and angiogenesis within endometrium (Moghaddam et al., 2022).
	CNR1	Allam et al., (2022) found significantly higher expression and a change in pattern of *CNR1* expression in ovarian endometriotic lesions compared to controls, using gene expression assays, concluding endometriosis-associated immune response and chronic pain is mediated by *CNR1*.
	KISS1R	*KISS1R* impacts follicular development, oocyte maturation, ovulation, and steroidogenesis (Hu et al., 2018).

	TACR3	Altering levels of *TACR3* may lead to increased adhesion, potentially within endometriotic cells outside the uterus leading to endometriosis implants and lesions through *TACR3* involvement in the phosphatidylinositol-calcium second messenger system (P-CSMS), activating cellular reaction through mobilising Ca(2+) in reaction to a stimulus via maintaining a low cytoplasmic Ca(2+) concentration (Joseph et al., 2014).

Within the heat maps only stages 2 and 3 of endometriosis were used, this was due to the low number of participants in stage 1 and 4 of endometriosis.

From the study cohort stage 3 endometriosis had a higher frequency of patients with the same variants compared to stage 2, this can be seen across the heatmaps produced (Figures 7 and 8, appendices 2-10.), indicating that multiple variants were the same within a high frequency of stage 3 endometriosis patients compared to other stages of endometriosis. This may be due to most of this cohort having stage 3 endometriosis.

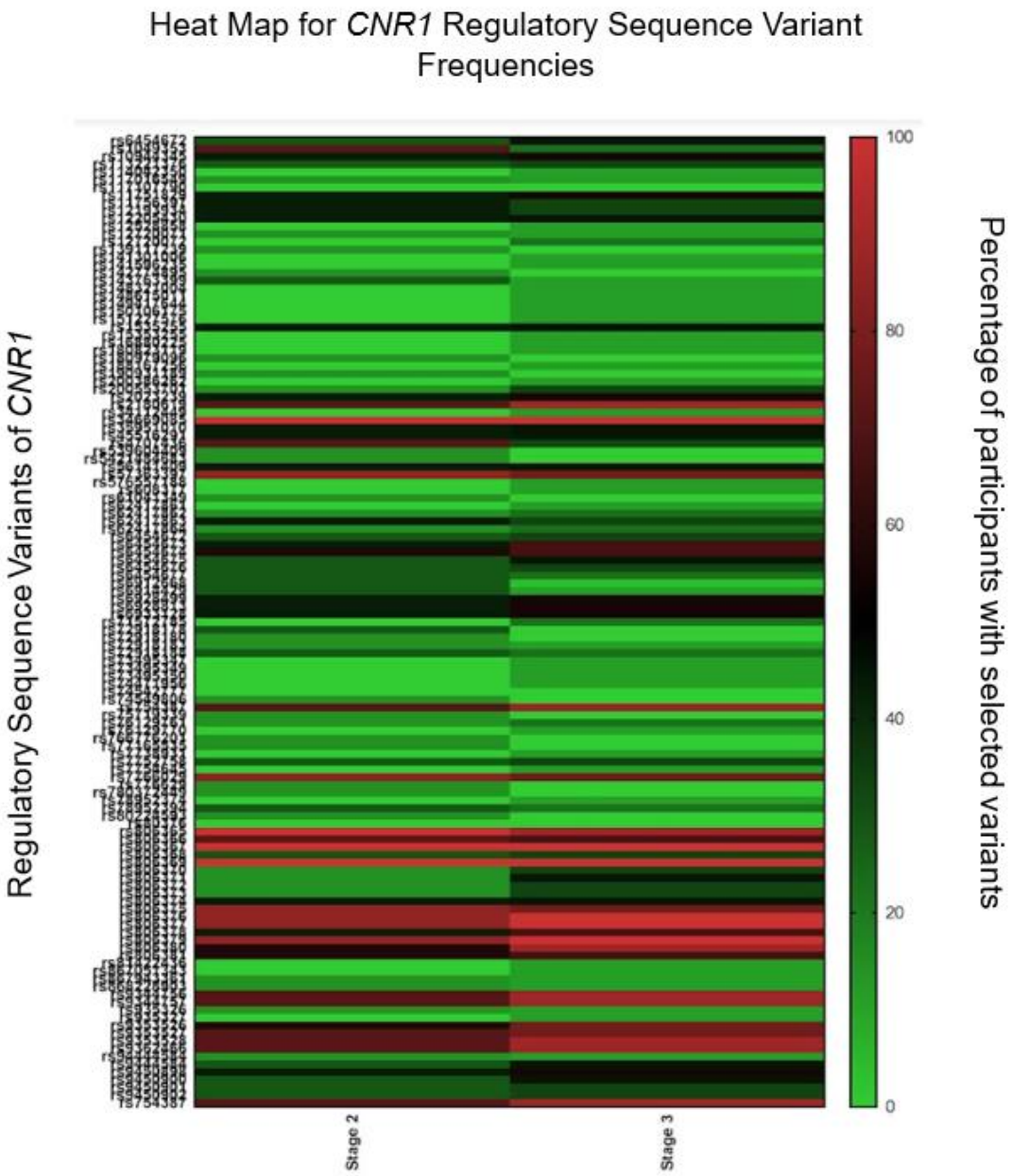

Figure 7: Heatmap presenting the frequency of *CNR1* regulatory sequence variants in endometriosis stages 2 and 3 in this cohort.

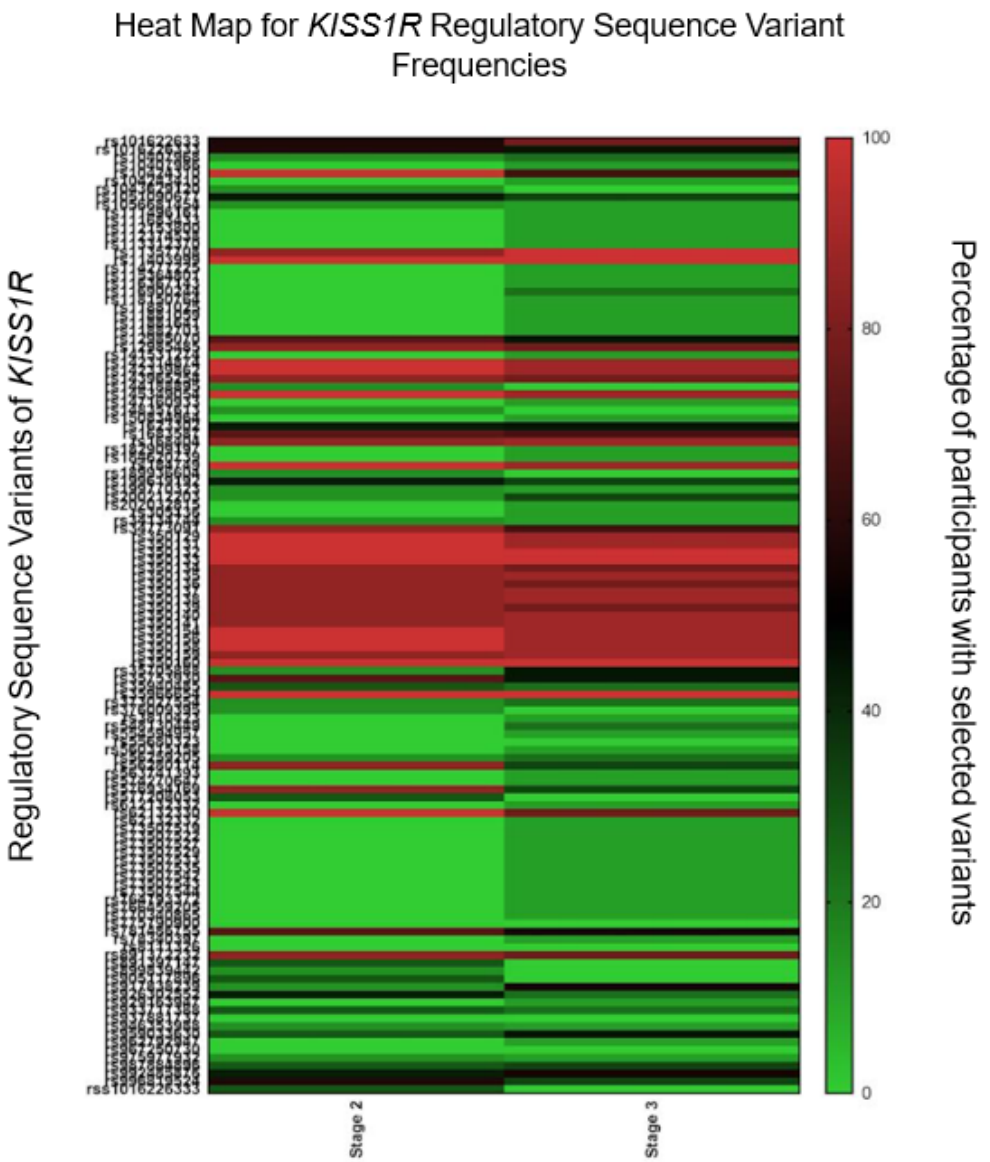

Figure 8: Heatmap presenting the frequency of *KISS1R* regulatory sequence variants in endometriosis stages 2 and 3 in this cohort.

The comparison of variants in the GE endometriosis (figures 7 and 8, appendices 2-10) and the general GE population identified ten SNPs, as potential contributors to endometriosis (seen in table 13). Nearly half the variants (four) found in this study showed a 0% frequency in Ensembl population but showed to be present in the GE population. This may be due to GE recruiting participants with specific diseases or known genetic conditions, causing a higher percentage of participants in GE with genetic mutations and variants compared Ensembl.

SNPs selected are more frequent within the endometriosis cohort from GE, compared to Ensemble and GE general populations (figure 9). Using table 13 and a χ^2 test using frequencies, variants rs806372, rs76129761, rs2069840, rs34880821, rs933717388, and rs72643906 are statistically significant between the endometriosis cohort and general population ($p<0.001$, where df is 1).

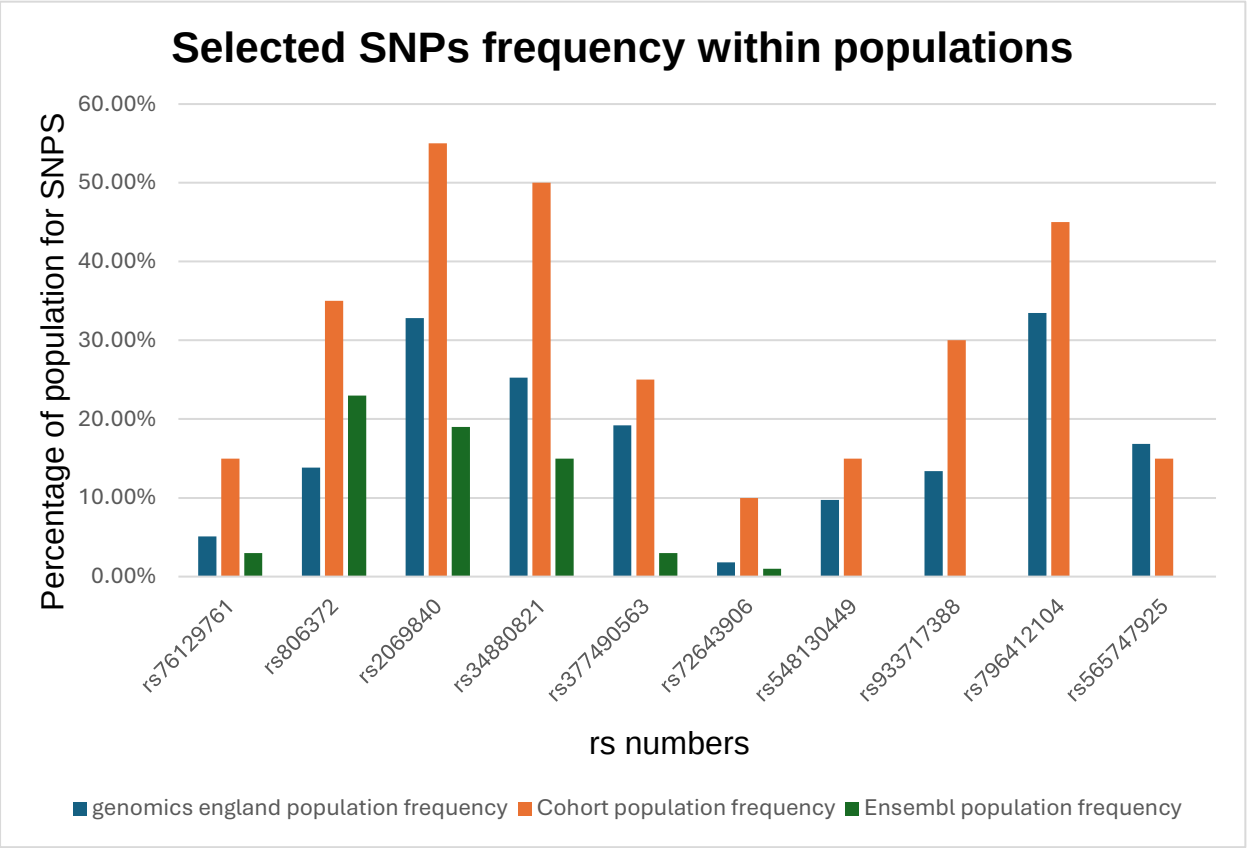

Figure 9: percentage of selected SNPs as found within this cohort, Genomic England population and Ensembl population.

Table 13: Comparison of variant frequencies using a χ^2 test using counts 1df and a P-value of 0.001, leading to a χ^2 value of over 10.827 to be significant. Significant variants are indicated with an asterisk. Comparison of variants using a χ^2 test using frequencies using 1df and a P-value of 0.001, leading to a χ^2 value of over 10.827 to be significant (these are indicated with an asterisk), and a χ^2 test using counts using

1df and a P-value of 0.05, leading to a χ^2 value of over 3.841 to be significant (these are indicated in yellow).

Rs number	Gene	Cohort population frequency	Genomics England population frequency	Standard deviation	Standard error	χ^2 value with frequencies with a 1 d.f. and a p-value of 0.001	Expected	Observed	χ^2 value with counts with a 1d.f. and a p-value of 0.05
rs76129761*	*CNR1*	15%	5.095%	7.000	4.95	19.217	0.96805	3	4.265090442
rs806372*	*CNR1*	35%	13.86%	14.948	10.57	32.243	2.6334	7	7.24052387
rs2069840	*IL-6*	55%	32.82%	15.683	11.09	14.989	6.24	11	3.631025641
rs34880821*	*IL-6*	50%	25.26%	17.493	12.37	24.23	4.7994	10	5.635337826
rs377490563	*IDO1*	25%	19.19%	4.108	2.905	1.759	3.6461	5	0.5031553375
rs72643906*	*IDO1*	10%	1.788%	5.805	4.105	37.655	0.33972	2	8.114122449
rs548130449	*KISS1R*	15%	9.749%	3.712	2.625	2.826	1.85231	3	0.7111079334
rs933717388*	*KISS1R*	30%	13.41%	11.730	8.295	20.524	2.5479	6	4.677182939
rs796412104	*TACR3*	45%	33.49%	8.138	5.755	3.955	6.3631	9	1.092744356
rs565747925	*TACR3*	15%	16.83%	1.294	0.915	0.198	3.1977	3	0.01222293836

When comparing the six significant variants in the endometriosis cohort compared to the random sample cohort and the total GE population, each of the variants are shown to be significantly higher in the endometriosis group. Except rs76129761 which is shown to be higher in the random sample cohort (see figure 10).

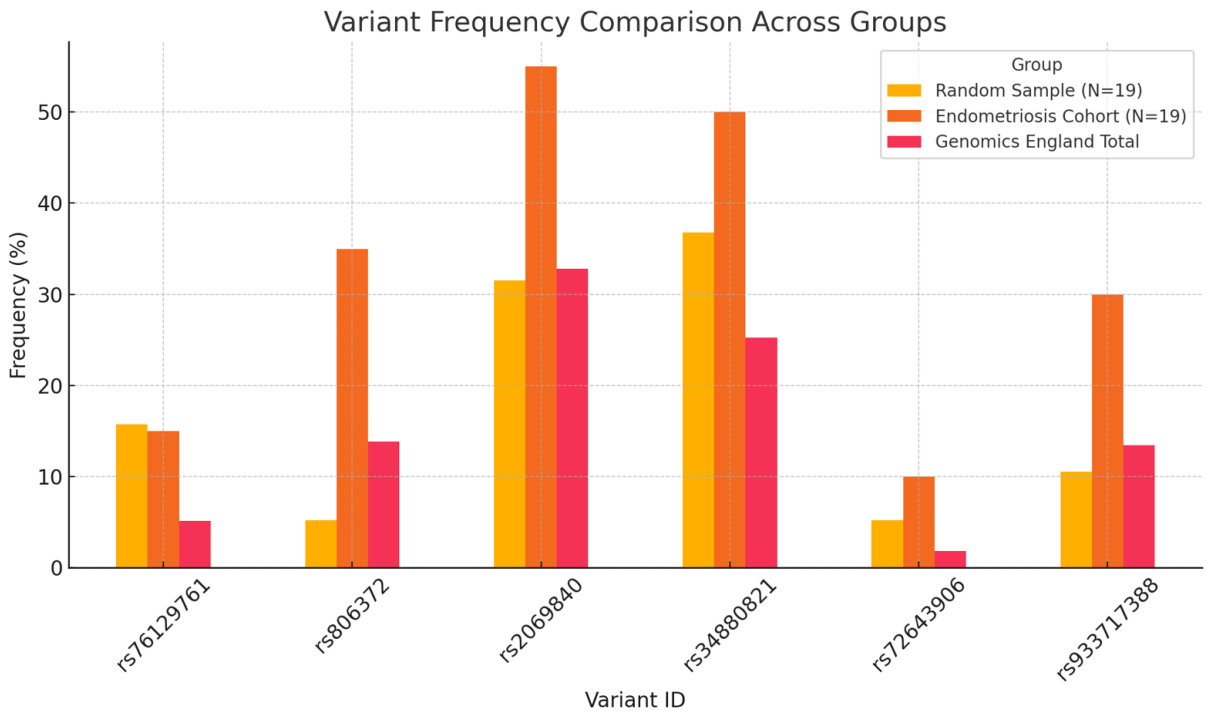

Figure 10: Variant frequency comparison against random sample, endometriosis cohort and GE total groups.

From the fisher's combined probability test between the endometriosis cohort and the random sample compared to the GE total population a combined χ^2 statistic and BH; 44.37, with a p-value of 0.000013 ($p < 0.001$) showed strong evidence in overall frequency difference between the endometriosis cohort and the GE total population across all endometriosis variants. This suggests that the genetic profile of the endometriosis cohort significantly deviates from the general population, potentially indicating a unique genetic signature associated with endometriosis. Furthermore, the combined χ^2 statistic and BH for the random sample cohort; 12.23, with a p-value of 0.427, showed no significant difference between the random sample cohort and the GE total population across all endometriosis variants (see tables 14 and 15). This lack of significant deviation suggests that the Random Sample's variant

frequencies are representative of the GE Total Population, serving as a control group.

Table 14: χ^2 Goodness-of-Fit Test results for each variant in both Endometriosis and Random cohorts compared to the GE total population.

Variant ID	Observed group	Expected group	Observed count	Expected count	χ^2 value	p-value	Interpretation
rs76129761	Endometriosis cohort	GE total population	3	0.9	5.143646408839780	0.023331593081759400	Moderate evidence of a significant difference in frequency for this variant.
rs76129761	Random sample	GE total population	3	0.9	5.143646408839780	0.023331593081759400	Moderate evidence of a significant difference in frequency for this variant.
rs806372	Endometriosis cohort	GE total population	7	2.6	8.626641651031900	0.003312817523356740	Strong evidence of a significant difference in frequency for this variant.
rs806372	Random sample	GE total population	1	2.6	1.140712945590900	0.285501728934225 00	No significant difference in frequency for this variant.

rs2069840	Endometriosis cohort	GE total population	11	6.24	5.4066996222168600	0.020059606754631400	Moderate evidence of a significant difference in frequency for this variant.
rs2069840	Random sample	GE total population	6	6.24	0.013744875813841400	0.906671025118980	No significant difference in frequency for this variant
rs34880821	Endometriosis cohort	GE total population	10	4.8	7.537558685446010	0.006042586245540780	Strong evidence of a significant difference in frequency for this variant.
rs34880821	Random sample	GE total population	7	4.8	1.3491784037558700	0.2454218007237800	No significant difference in frequency for this variant.
rs72643906	Endometriosis cohort	GE total population	2	0.3	9.787878787878790	0.001756659900877229	Strong evidence of a significant difference in frequency for this variant.
rs72643906	Random sample	GE total population	1	0.3	1.6595365418894800	0.1976659106582800	No significant difference in

							frequency for this variant.
rs933717388	Endometriosis cohort	GE total population	6	2.5	5.642424242424240	0.017530950708949900	Moderate evidence of a significant difference in frequency for this variant.
rs933717388	Random sample	GE total population	2	2.5	0.11515151515151500	0.7343537463979000	No significant difference in frequency for this variant.

Table 15: BH correction results

Variant ID	**Original p-value (Endometriosis)**	**BH-corrected p-value (Endometriosis)**	**Original p-value (Random Sample)**	**BH-corrected p-value (Random Sample)**
rs76129761	0.023	0.046	0.023	0.092
rs806372	0.003	0.018	0.285	0.570
rs2069840	0.020	0.040	0.907	0.907

rs34880821	0.006	0.024	0.245	0.490
rs72643906	0.001	0.006	0.198	0.396
rs933717388	0.018	0.036	0.734	0.734

Table 16: Comparison of expected and observed in the endometriosis cohort of this study using dbSNP population frequencies in varying ethnicities for each of the significant variants found.

Variant	**Gene**	**Ethnicities**	**Expected value in cohort (as seen in dbSNP)**	**Observed value in cohort**
rs72643906	*IDO1*	European	0.00441	Observed
		Asian	0.000	Not observed
		African	0.0007	Not observed
		Total	0.00386	**Observed**
rs933717388	*KISS1R*	European	0.0026	Observed
		Asian	0.000	Not observed

		African	0.0085	Not observed
		Total	0.00370	**Observed**
rs34880821	*IL-6*	European	0.26536	Observed
		Asian	0.054	Not observed
		African	0.1051	Not observed
		Total	0.22071	**Observed**
rs2069840	*IL-6*	European	0.33686	Observed
		Asian	0.054	Not observed
		African	0.1521	Not observed
		Total	0.30666	**Observed**
rs76129761	*CNR1*	European	0.03872	Observed
		Asian	0.000	Not observed
		African	0.0252	Not observed
		Total	**0.03591**	**Observed**
rs806372	*CNR1*	European	0.11585	Observed
		Asian	0.455	Not observed

		African	0.0896	Not observed
		Total	**0.12197**	**Observed**

Table 16 shows the endometriosis cohort in this study has a higher significant variant frequency in European (white) ethnicities and the total cohort when compared to the expected frequencies as determined by dbSNP. However, the African and Asian ethnicity populations in this cohort did not have these variants, with five variants (rs806372, rs2069840, rs210018116, rs933717388 and, rs72643906) observed in this cohort in other ethnic groups or the patient's ethnicities were not stated.

Using UCSC (2023) each of the significant variants were searched to create a variant profile as seen in Table 17. More information on each variant profile can be seen in Sections 3.4 to 3.9.

Table 17: Variant profiles for the significant variants found within this cohort (created using UCSC (2023)).

Variant	**Associated gene**	**Variant type**	**Chromosome location**	**Variant consequence**	**Transcription factor (TF) binding site affected (if applicable**	**Number of publications**	**Conservation rate**	**Splicing sites**	**Pollutant interference**
rs72643906	*IDO1*	Downstream variant	Chr8:39779157-399779157	A has changed to G	*ZIC2 (*Zic family member 2)	None	Highly conserved in mammals and vertebrates	None	BPA and TBBPA can decrease methylation of *IDO1*'s mRNA and DNA (Merrill et al., 2023), and TCDD can increase IDO1 expression levels (Matta et al., 2021). Exposure to BPA has been shown to

									decrease *ZIC2* expression (Brown, 2009).
rs933717388	*KISS1R*	Intron variant	Chr19:912365-912365	C has changed to G	*ZNF707 (*Zinc finger protein 707*)* and *ZBTB11 (*Zinc finger and BTB domain-containing protein 11*)*	None	Conserved in humans	None	DEHP exposure influences regulators of HPGA by regulating GnRH release altering *KISS1R* expression (Xie et al., 2022).
rs34880821	*IL-6*	Intergenic	Chr7:22775450-22775450	G has changed to A	None	3	Conserved in humans	None	Exposure to TCDD can increase the expression of *IL-6* (Matta et al. 2021).
rs2069840	*IL-6*	Intronic	Chr7:22768572-22768572	C has changed to G	None	12	Conserved in rhesus,	None	Exposure to TCDD can increase the

							mouse, and dogs.		expression of *IL-6* (Matta et al. 2021).
rs76129761	*CNR1*	Intron	Chr6:88860156-88860156	CTCT has changed to CT	*ZNF701 (*Zinc finger protein 701*), SOX4 (SRY-box transcription factor 4), SOX6 (SRY-box transcription factor 6), FOXD3 (*Forkhead box D3*)* and *SOX11 (SRY-box transcription factor 11).*	None	Conserved in human, rhesus, mouse, and dogs.	None	Exposure to DiNP and BPA significantly increased the expression of *CNR1* (Forner-Piquer et al., 2018). Exposure to BPA can upregulate *SOX4* expression (Kang et al., 2014), *SOX6* and *SOX11* (Lichtensteiger et al., 2021). Exposure to BPA has been shown to decrease *FOXD3*

									levels (Baba et al., 2009).
rs806372	*CNR1*	Intron	Chr6:88846563-88866563	C has changed to G	*SOX12 (SRY-box transcription factor 12).*	3	Conserved in humans and rhesus.	SIB locus ID: NC-000006-1470. 3 alternative transcripts within intron 1 (6q15) of *CNR1*.	Exposure to DiNP and BPA significantly increased the expression of *CNR1* (Forner-Piquer et al., 2018). DEHP can increase *SOX12* expression levels (Chou et al., 2019).

Each of the significant variants were found to be common within specific tissues (figure 11). Variants rs72643906, rs34880821 and rs2069840 were found to be common in patients with endometriosis of the pelvic peritoneum. All the variants were consistent in patients with unspecified endometriosis and endometriosis of the ovary. Three variants (rs72643906, rs933717388 and rs76129761) were found to be common in patients suffering from endometriosis of the uterus. Only two variants (rs2069840 and rs806372) were found to be in patients with endometriosis of the intestine (however, endometriosis of the intestine only showed in <5 of the IVA cohort).

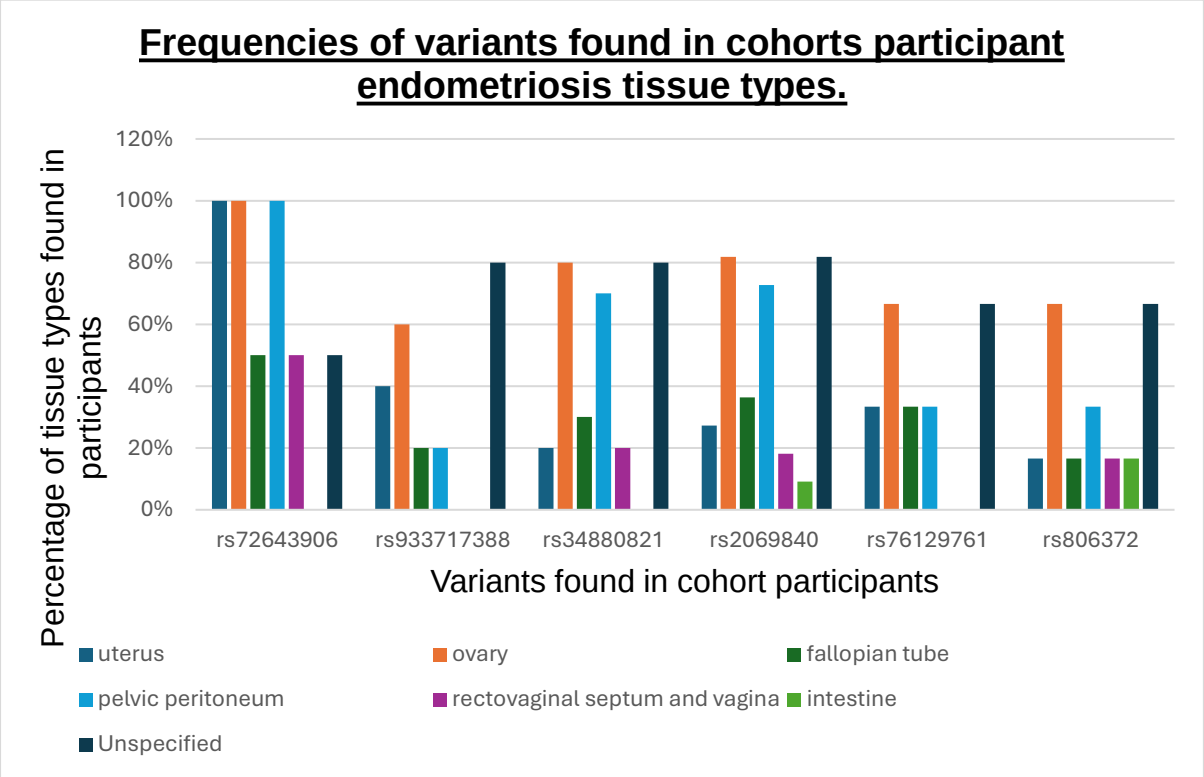

Figure 11: Frequency of tissue types found in this cohort population with significant variants.

3.4 Genomic findings of the rs72643906 variant and potential consequences

UCSC research shows rs72643906 may impact upon the TF *ZIC2*. Although string (Szklarczyk et al., 2023) found no direct interactions between *IDO1* and the TF *ZIC2*, it can be hypothesised that the *IDO1* variant rs72643906 potentially prevents *ZIC2* binding due to having a motif, it is possible it has not been investigated. The consequence is potentially through changing the base pairs preventing the TF from knowing where to bind. Potentially increasing the expression of both *IDO1* and *ZIC2*. When the EDC BPA is introduced to the pathway through the environment, it can decrease *ZIC2* and *IDO1* expression (figure 12).

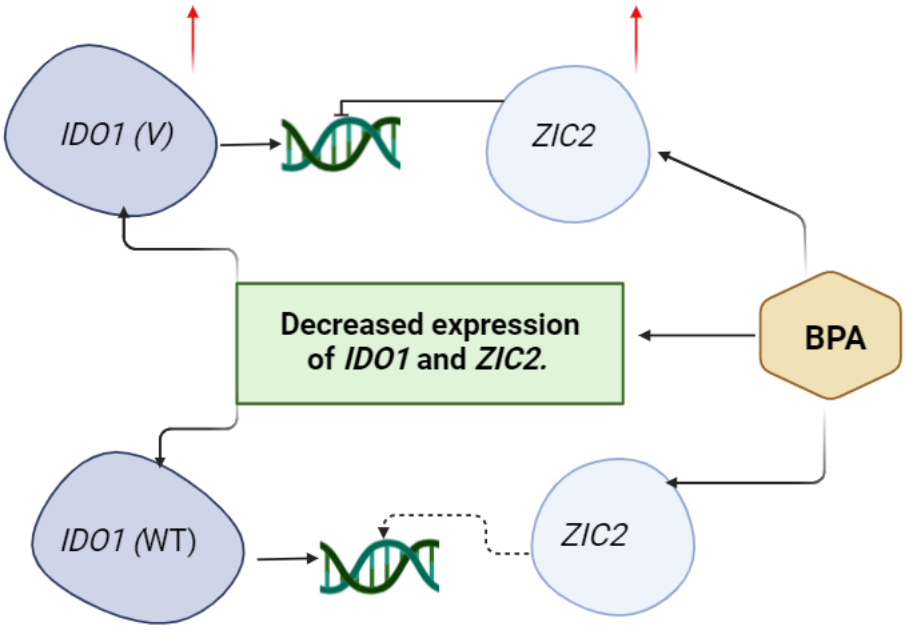

Figure 12: Hypothesised pathway for disrupted ZIC2 binding through the rs72643906 variant, and further disruption from EDC BPA. With V for variant, and WT for wild type.

3.5 Genomic findings of the rs806372 variant and potential consequences

UCSC (2023) research shows rs806372 is a Denisovan variant, meaning the variant is more prevalent in east Asian populations (UCSC, 2023; Reich et al., 2019; Meyer et al., 2012). UCSC (2023) research has also shown this variant may impact upon the TF *SOX12* binding start site. Although, string found no direct interactions between *CNR1* and *SOX12*, it can be hypothesised that rs806372 variant of the *CNR1* gene potentially prevents the binding of *SOX12*, through the consequence changing the base pairs preventing the TF finding the location of binding, potentially increasing *CNR1* expression and decreasing *SOX12* expression. Furthermore, when DEHP is introduced to the pathway through the environment the expression of both *CNR1* and *SOX12* are increased (figure 13).

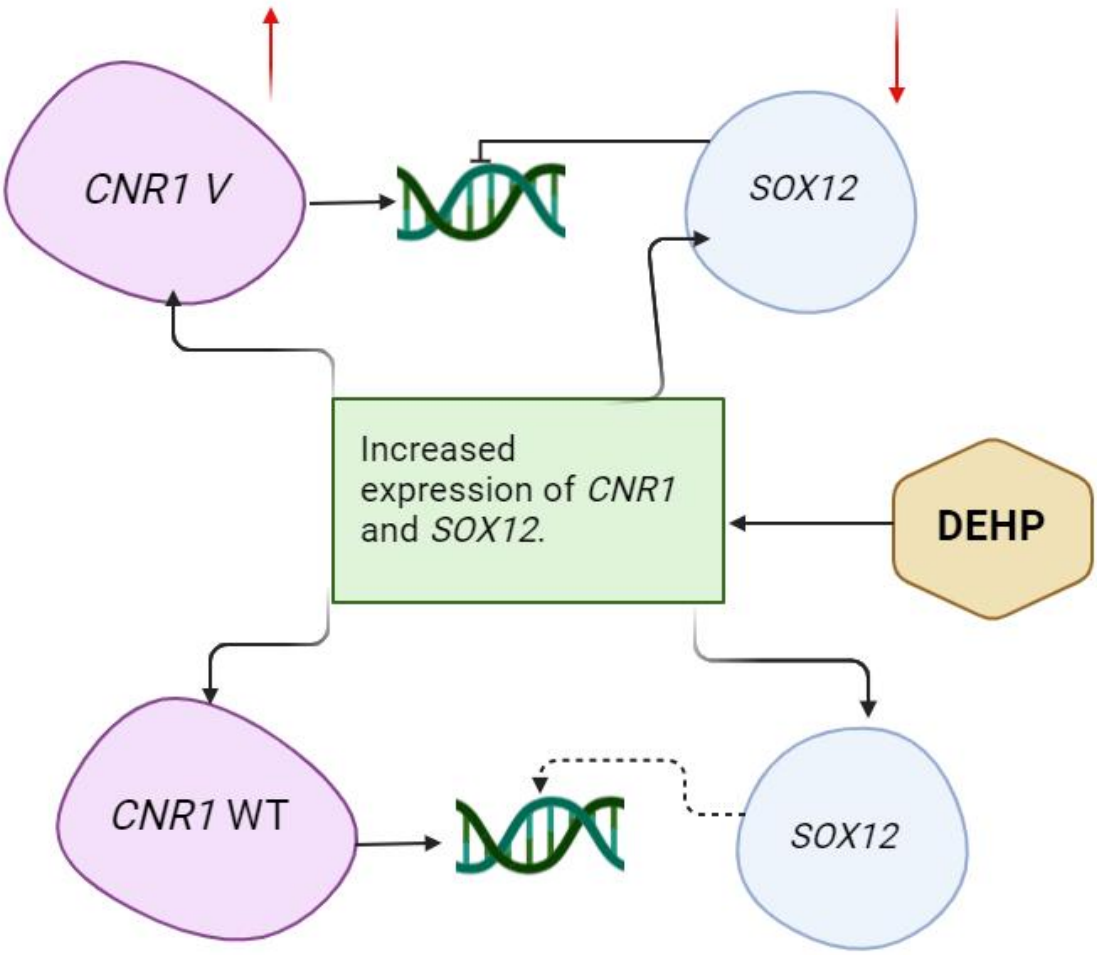

Figure 13: Hypothesised pathway for disrupted *SOX12* binding through the rs806372 variant, and further disruption from EDC DEHP.

3.6 Genomic findings of the rs76129761 variant and potential consequences

UCSC research shows five TF potentially impacted by rs76129761. These TF are *ZNF701*, *SOX4*, *SOX6*, *FOXD3* and *SOX11*. Although string found no direct interactions between *CNR1* and the TF *ZNF701*, *S0X4*, *S0X6*, *FOXD3* and *SOX11*. It is possible to hypothesize potential consequences of *CNR1* variant rs76129761 and TF, through the consequence changing the base pairs preventing the TF from knowing where to bind. It can be hypothesized that rs76129761 inhibits the binding of *ZNF701*, in turn increasing the expression of these genes (figure 14). Although *CNR1* expression is also increased when exposed to the EDC DEHP, there is no current information for the effects of EDC's on *ZNF701*.

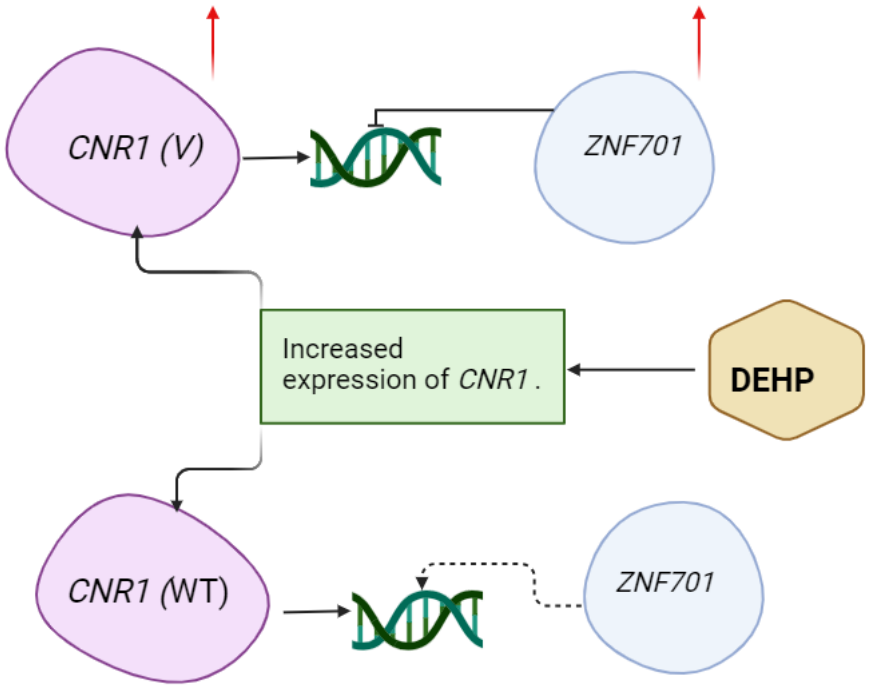

Figure 14: Hypothesised pathway for disrupted *ZNF701* binding through the rs76129761 variant, and further disruption from EDC DEHP.

It can be hypothesized that rs76129761 inhibits the binding of *SOX4*, in turn increasing the expression of *CNR1* and *SOX4*. Furthermore, the EDC BPA has been shown to upregulate both *CNR1* and *SOX4* (figure 15).

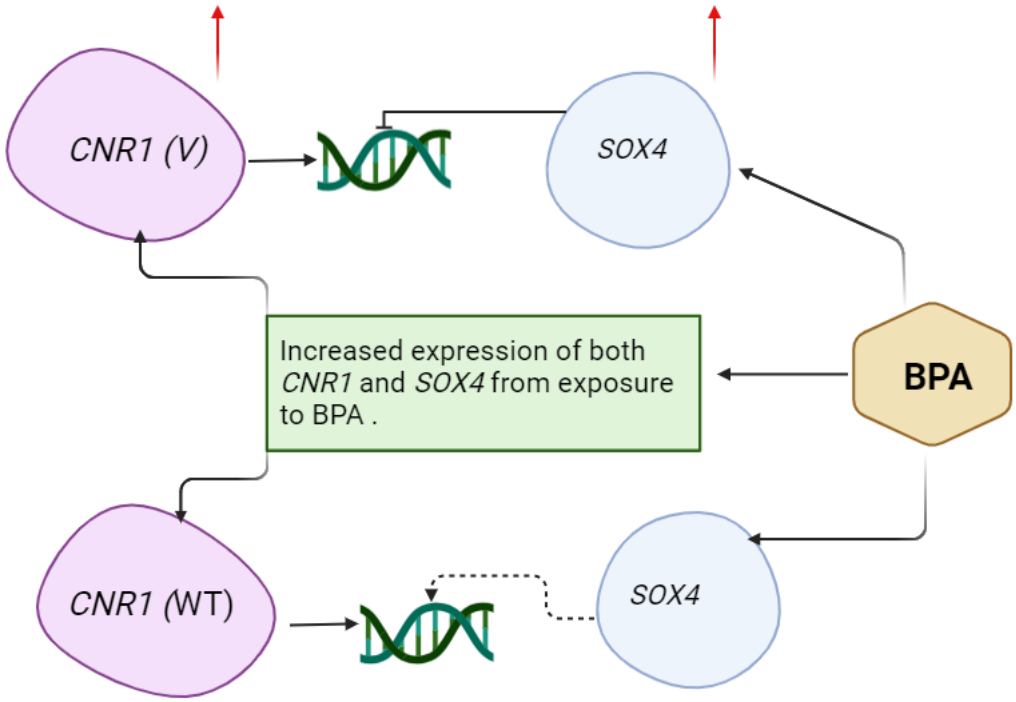

Figure 15: Hypothesised pathway for disrupted *SOX4* binding through the rs76129761 variant, and further disruption from EDC BPA.

The variant rs76129761 potentially inhibits the binding of *SOX6*, in turn increasing the expression of *CNR1* and decreasing *SOX6*. Furthermore, the EDC BPA has been shown to upregulate both *CNR1* and *SOX6* (figure 16).

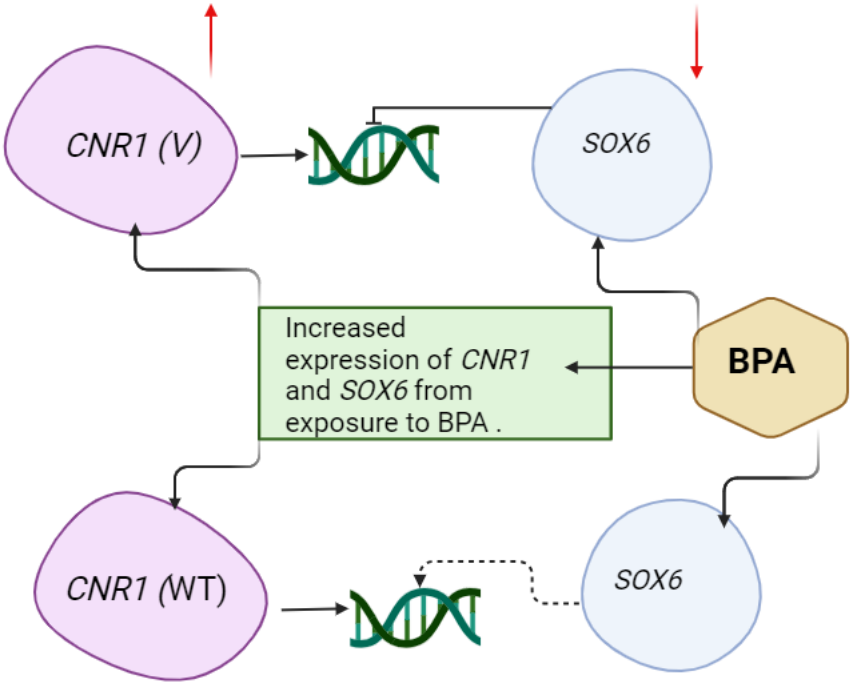

Figure 16: Hypothesised pathway for disrupted *SOX6* binding through the rs76129761 variant, and further disruption from EDC BPA.

It is possible that rs76129761 inhibits the binding of *FOXD3*, in turn increasing the expression of both *CNR1* and *FOXD3*. Furthermore, BPA has been shown to upregulate *CNR1* expression and downregulate the expression of *FOXD3* (figure 17).

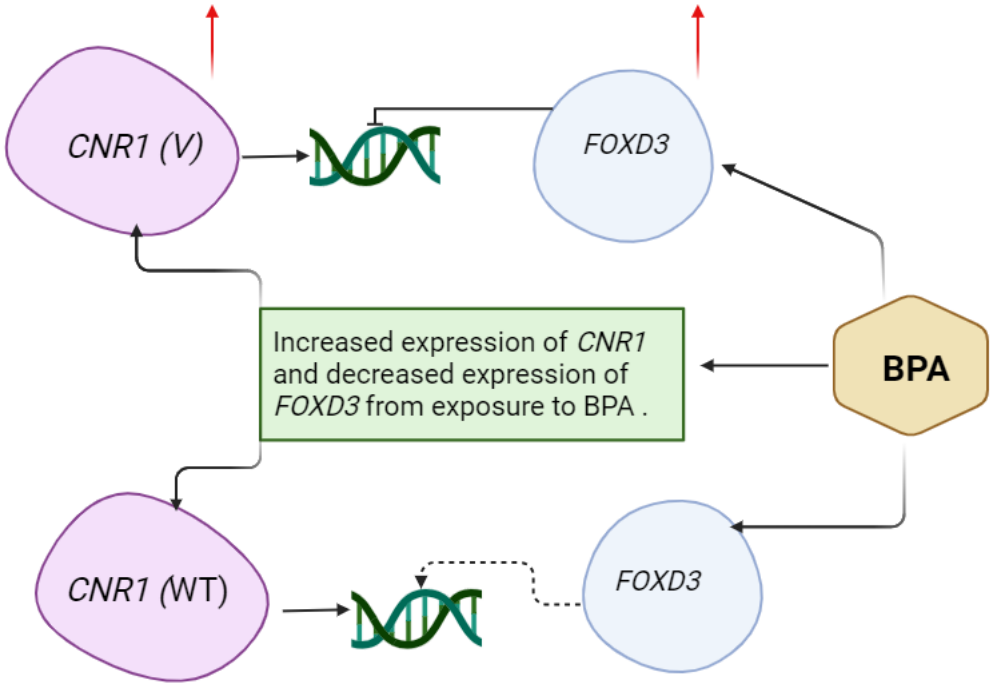

Figure 17: Hypothesised pathway for disrupted *FOXD3* binding through the rs76129761 variant, and further disruption from EDC BPA.

It can be hypothesised that rs76129761 inhibits the binding of *SOX11*, in turn increasing the expression of both *CNR1* and *SOX11*. Furthermore, the EDC BPA has been shown to upregulate the expression of both *CNR1* and *SOX11* (figure 18).

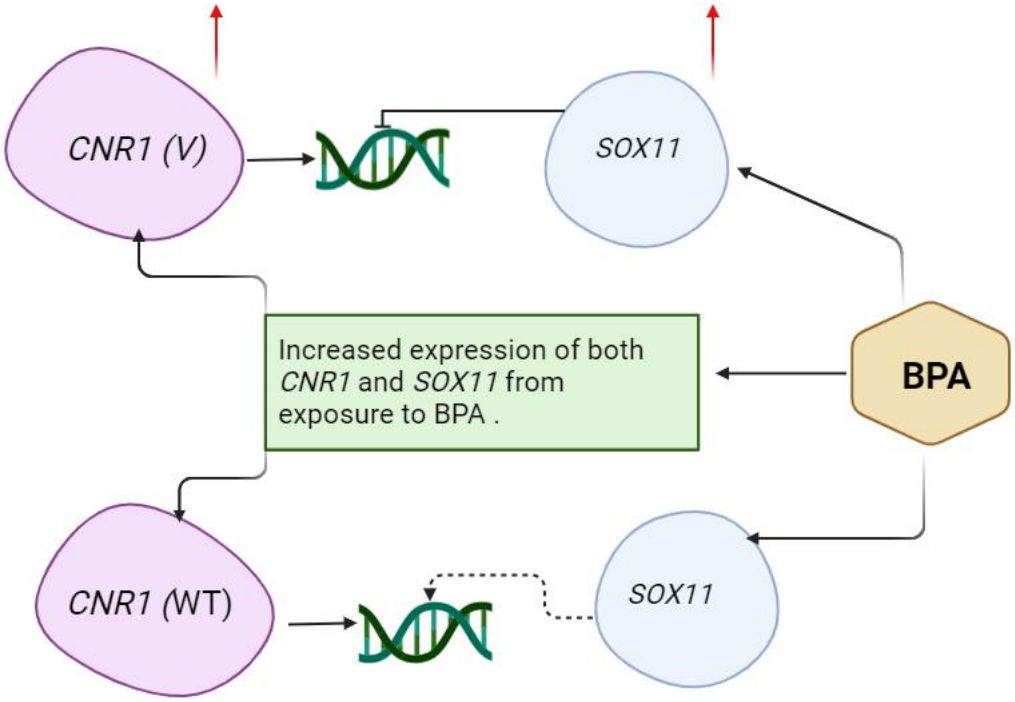

Figure 18: Hypothesised pathway for disrupted *SOX11* binding through the rs76129761 variant, and further disruption from EDC BPA.

3.7 Genomic findings of the rs34880821 variant and potential consequences

UCSC research showed that rs34880821 is a Neanderthal variant (UCSC, 2023; Briggs et al., 2007; Green et al., 2010) (figure 19).

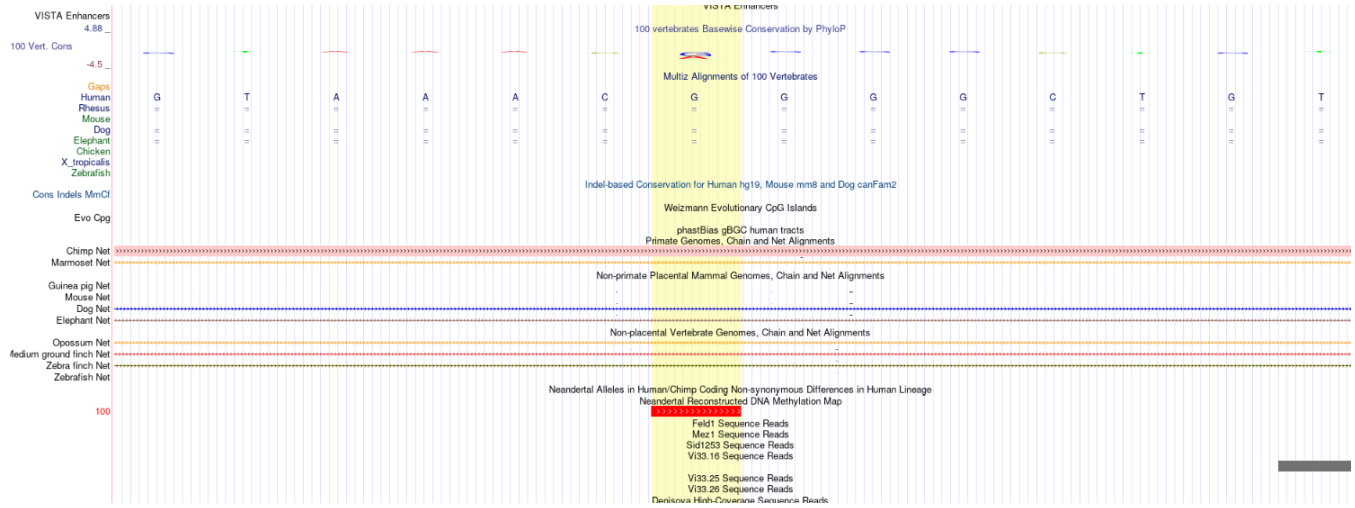

Figure 19: The rs34880821 falls within the neanderthal region as seen by the red line representing 100% methylation for CpG position from the neanderthal reconstructed DNA methylation map (UCSC, 2023; Briggs et al., 2007; Green et al., 2010).

3.8 Genomic findings of the rs2069840 variant and potential consequences

This variant is an intronic variant conserved in rhesus, mice, and dogs (figure 20), and is high in Estonian, Vietnamese, and Korean populations. However, UCSC (2023) research found no splicing sites or TF sites.

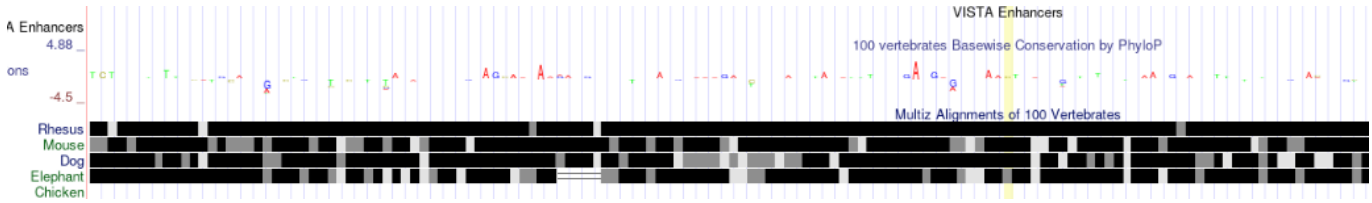

Figure 20: Conservation rate for rs2069840 (UCSC, 2023).

3.9 Genomic findings of the rs933717388 variant and potential consequences

UCSC research shows two transcription factors which are potentially impacted by rs933717388. These transcription factors are *ZNF707* and *ZBTB11.* Although string found no direct interactions between *KISS1R* and *ZNF707* and *ZTB11*. It is possible to hypothesize potential consequences of *KISS1R* variant rs933717388 and TF, through the consequence changing the base pairs preventing the TF from knowing where to bind. It can be hypothesized that rs933717388 inhibits the binding of *ZNF707* and *ZBTB11*, in turn increasing the expression of these genes (figures 21 and 22). Although *KISS1R* expression is also increased when exposed to the EDC DEHP, there is no current information for the effects of EDC's on *ZNF707* and *ZBTB11*.

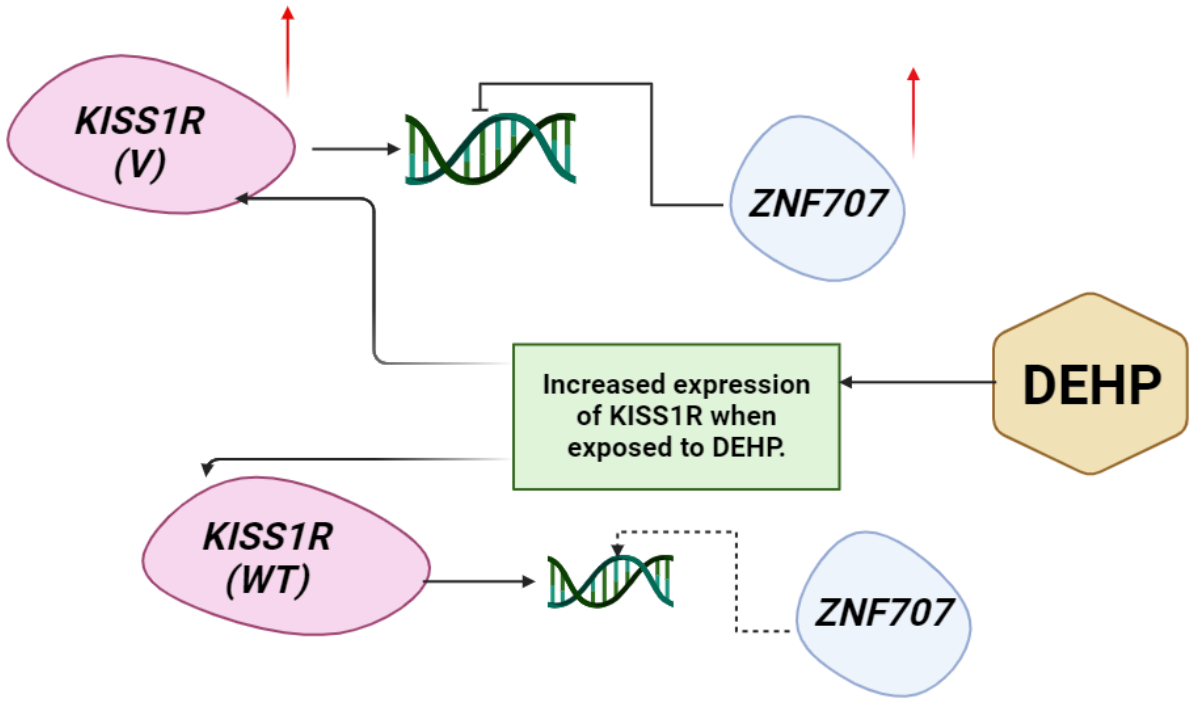

Figure 21: Hypothesised pathway for disrupted *ZNF707* binding through the rs933717388 variant, and further disruption from EDC DEHP.

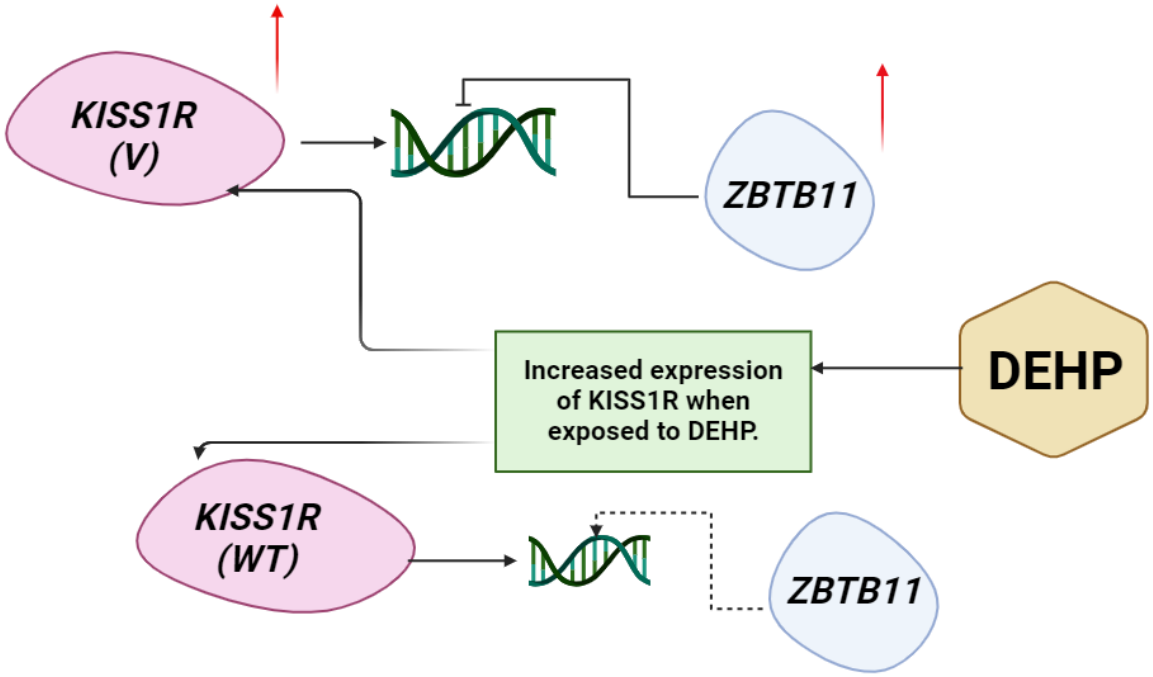

Figure 22: Hypothesised pathway for disrupted *ZBTB11* binding through the rs933717388 variant, and further disruption from EDC DEHP.

Through observing the literature found using the methods in section 2.2 and results obtained through using the methods in sections 2.3-2.7, a clear understanding of processes related to endometriosis can be seen. Figure 23 shows a visual understanding of the pathways, tissues, genes, TFs, and environmental pollutants which may influence endometriosis onset and progression.

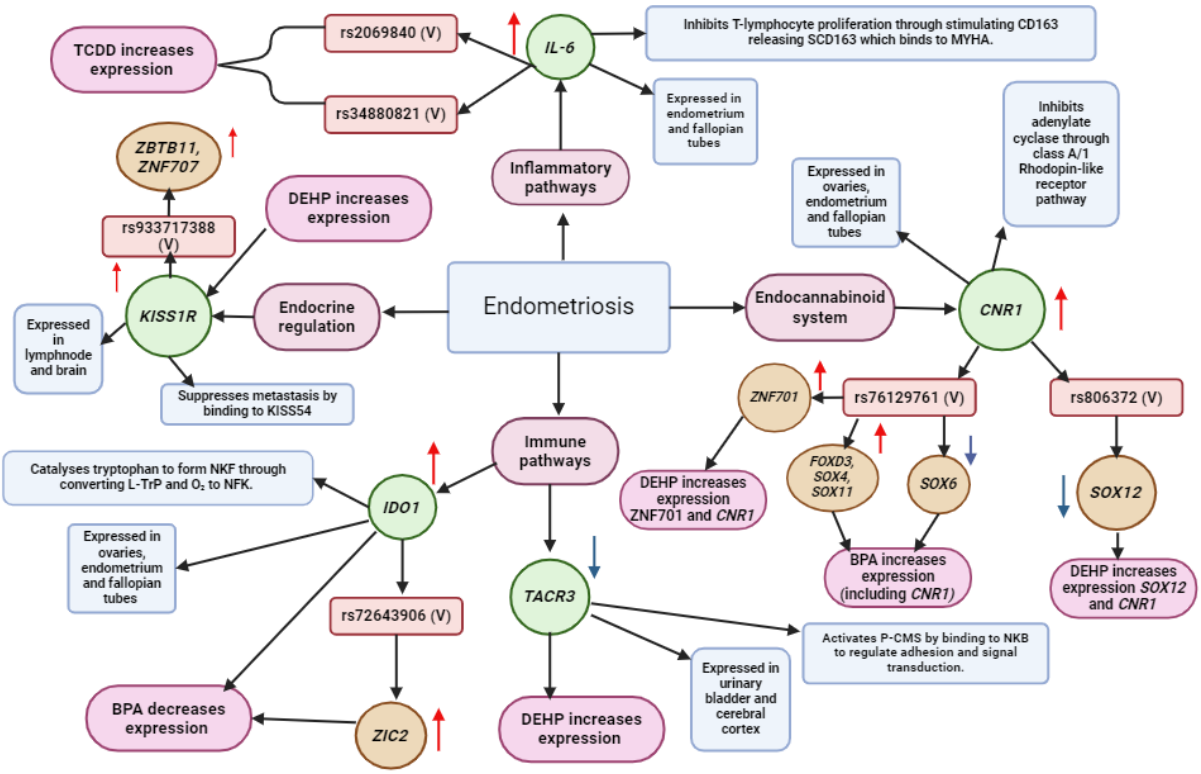

Figure 23: A visual representation of components found to potentially relate to endometriosis onset and progression. The red arrows represent potential increased expression levels of genes, blue arrows represent potential decreased expression of genes, and TFs in endometriosis patients, green circles represent genes, orange circles represent TFs, blue squares represent properties of each gene, light pink boxes represent pathways, light purple boxes represent EDCs effect on genes and TFs and light red boxes represent variants.

4.0 Discussion

4.1 Participant details

When observing the results, stages 1 and 2 of endometriosis had the oldest participants averaging at 38 and 39 years old respectively, compared to stages 3 and 4 where patients had an average age of 36 years old. These observations do not correlate to previous literature as endometriosis is progressive if not treated, with worsening symptoms overtime, notably Meyers hypothesized that endometriosis increases with age (reviewed in Dou et al., 2019; Pandey et al., 2021).

A potential explanation for this observation is through onset of endometriosis through environmental factors, with disruption of hormone signalling, secretion and metabolism from EDC exposure may lead to onset of endometriosis in older patients (La Merrill et al., 2020). DEHP exposure can alter the ECS causing upregulation of inflammatory and pain processes and metabolising enzymes related to angiogenesis (Barrie and Manolios, 2017), potentially leading to endometriosis development in older women. Bacterial infections, specifically *fusobacterium* (see appendix 1a), may also to lead to endometriosis onset through structural changes within endometrial tissues outside the uterus, potentially resulting in older patients having less severe stages of endometriosis, enabling speculation that younger patients with more severe stages of endometriosis may be through genetic factors.

Severe stages of endometriosis were identified relatively sooner than earlier stages of endometriosis, with average diagnosis age of 30 (stage 3), 29 (stage 4), and 31 (stages 1 and 2). This may be due to updated ESHRE guidelines, stating endometriosis will not be diagnosed through biomarkers and current imaging techniques do not show superficial or early stages of endometriosis (see table 3, section 1.3 for ESHRE-guidelines) (Becker et al., 2022), possibly preventing early-stage diagnosis. Within this cohort 38% of women underwent a laparoscopy to diagnose endometriosis with <35% of participants undergoing cauterisation of endometriotic lesions. This may be due to women with debilitating symptoms of endometriosis seeking diagnosis through a laparoscopy as a last resort, whereas patients with less severe stages of endometriosis may not wish to undergo a laparoscopy due to associated risks (seen in section 1.3) (Koninckx et al., 2021).

These factors may prevent patients from being diagnosed, demonstrating why new, less invasive forms of diagnosis are required.

Within this cohort 86% of patients had endometriosis located within ovaries (ovarian endometriomas) making it the most common location, whilst other studies found endometriosis located in intra-pelvic site, specifically ovaries, is the most common form of endometriosis (Chang et al., 2022; Arafah et al., 2021). Chandra and Chaudhary, (2021) found 44% of endometriosis patients to have ovarian endometriomas. The least common location was in intestines in <5 of cohort cases. This is atypical due to the location being in an extra-pelvic site outside and away from gynaecological organs (Chen et al., 2023). This location may be more common due to the complex nature of diagnosing extra-pelvic locations and may be missed (Bazot et al., 2021), with Yu and Joo (2022) finding diagnosis of extra-pelvic endometriosis is not routine, increasing likelihood of misdiagnosis.

The lack of ethnic variation in this study may be through the inability of minority demographics to access adequate healthcare or facing accessibility, cognitive, financial barriers, and historical bias (Duran-Kirac et al., 2022). A 1950's studies suggested a lower rate of endometriosis within black patients (Bougie et al., 2022). This unjust bias may have led to less minority demographics being diagnosed aiding in 72% of the cohort classified as white British.

4.2 57 potential genes influencing endometriosis onset found from the literature review.

Dysregulation of patterns within tissue-specific arrangement of gene expression can cause different diseases within tissues, with gene expression varying more within tissues when compared to an individual (Aguet and Ardlie, 2016). Results found 60% of genes expressed in endometrium tissue which is notable as a pre-courser of endometriosis (Kobayashi et al., 2017). Also 50.8% of genes in this study were expressed in ovaries. Papageorgiou et al., (2023) found a different gene expression in ovarian endometriosis in comparison to other manifestations of the disease. Genes expressed within endometrial tissue may differ to genes expressed within the ovary. It is plausible that genes found in this literature search may cause

dysregulation within tissues prominent in endometriosis patients potentially causing onset and progression of endometriosis.

Studies have shown that each of these genes may be associated with endometriosis predisposition with table 11 giving further data that variants within these genes are prominent within endometriosis cases. The genes identified in this research (table 18) contain multiple variants and the findings of this work show these genes may be associated to endometriosis, and these variants may also affect a pathway leading to endometriosis.

Table 18: Studies and conclusions of genes identified in this research.

Paper reference	**Gene/s involved**	**Conclusion of paper**
Adewuyi et al., 2020	*ARL14EP, TRIM32*	Some genetically controlled pathways may underlie endometriosis, with these genes showing genome-wide significance for the relationship between endometriosis and migraines.
Adewuyi et al., 2022	*MFHAS1, RABGAP1L, SMAD3, TNKS, SKAP1, WNT4*	The genes found in this paper had a genome-wide significance for endometriosis and asthma. Showing a significant association of a genetic susceptibility for asthma and endometriosis.
Allam et al., 2022	*CNR1*	This gene was found to have a significantly higher

		expression in ovary endometriotic lesions and is associated with immune response and chronic pain medication.
Benjamin et al., 2020	*IL-6*	Significantly higher levels of this gene were found in the peritoneal fluid of endometriosis patients showing this altered level may influence endometriosis patients through altered inflammatory responses.
Blasco et al., 2020	*KISS1, KISS1R, TAC3, TACR3*	Altered expression was found in these genes within endometriosis patients compared to healthy patients.
Cardoso et al., 2020	*CDKN2B-AS1, ETAA1, IL1A, NFE2L3, RND3, VEZT, WNT4, FN1*	Higher frequencies of these genes found in endometriosis patients. With these genes potentially influencing pathway functions and possibly the development of endometriosis.
Gallagher et al., 2019	*WNT4, CDC42, FSHB, GREB1, ESR1*	These genes were found in association with both endometriosis and uterine leiomyomata suggesting a

		potential genetic overlap origin.
Li et al., 2021	*KIF3A, KRAS, MDM2, SCAF11*	These genes were found to drive proliferation of endometrial cells and endometriosis.
Mear et al., 2020	*GSTM-1, IFNG*	These genes have a positive association to endometriosis, with polymorphisms within these genes showing a potential predisposition to endometriosis development.
Mortlock et al., 2022	*FN1, GREB1, CBX1, ID4, KDR, NFE2L1*	Expression rates were found to differ between endometriosis patients and controls in this study.
Painter et al., 2018	*KITLG, KLF3, LMO7, PARP11, PDZRN3, PRIM2, PTPRD, TFAP2D, ZNF536*	This paper found an association between these genes and co-occurrence with endometriosis and ovarian cancer.
Papageorgiou et al., 2023	*CEP112*	This paper concluded polymorphisms in this gene can alter estrogen metabolisms and therefore, exert endometriosis risk.

Perini et al., 2023	*CYP2C19*	This paper found that variants within this gene influences estrogen metabolism causing endometriosis risk.
Rahmioglu et al., 2023	*BMF, BSN, GDAP1, NFG, SRP14, MLLT10*	Methylation and expression changes in the regulation of these genes have been seen to be associated with maintenance and perception of pain, and therefore, show a correlation between inflammatory conditions and endometriosis.
Tanha et al., 2022	*IDO1*	This paper found altered expression of this gene in endometriosis patients meaning this gene may be involved in the pathogenesis of endometriosis through modulating inflammatory responses.
Wei et al., 2019	*NAT2*	Variants in this gene were found to be associated with a decreased risk of endometriosis. With Asian populations showing an increased endometriosis

		risk when *NAT2* gene has a slow acetylation phenotype. Furthermore, varying mutations of this gene may be involved in differing endometriosis risk through changes in enzyme function.
Zhai et al., 2019	*COMT*	This paper found that the incidence of endometriosis may be predicted by this gene's polymorphisms.
Zhang and Wang, 2023	*PGR*	Abnormal signalling and expression of this gene may lead to progesterone resistance in endometriosis patients.
Zubrzycka et al., 2020	*GREB1, ESR1, CYP17A1*	Identified significant loci in these genes which may lead to a risk in the development of endometriosis.

The genes found are a potential genetic component to the onset and progression of endometriosis, through dysregulation of patterns within tissue-specific arrangement of gene expression. This may lead to endometriosis, specifically genes expressed within ovaries and endometrium, directly impacting on pathways involved in immune and inflammatory systems, pain perception and management. Therefore, it can be speculated that endometriosis has a potential genetic component.

4.3 Environmental influence on a genetic susceptibility to developing endometriosis.

Many environmental factors can influence a person's genetic buildup through disruption and damage to genomes and metabolic processes. Chemical exposure, specifically environmental exposure of air pollution and man-made chemicals have been shown to correlate with an elevated risk of developing endometriosis (Zhang et al., 2021).

DEHP is an organic compound which is a diester of phthalic acid and falls within the phthalates class of EDCs (Lamraoui et al., 2020). DEHP makes plastics flexible and soft and is mainly used as a plasticiser for polyvinyl chloride (PVC) and medical devices (Rowdhwal and Chen, 2018).

DEHP exposure has been positively correlated with female infertility through interfering with typical ovarian functions, causing decreased steroidogenesis and premature ovarian failure, hence resulting in infertility (Zhan et al., 2022). DEHP toxicants can decrease ovarian mRNA and enzyme activities, disrupting normal antral follicle function and depletion of estrogen and progesterone (Hannon and Flaws, 2015). Alterations to ECS function, and associated effects of bioactive lipids cause unregulated activation of inflammatory and pain processes, increasing the risk of endometriosis development from bioactive lipids (Barrie and Manolios, 2017). This is through DEHP upregulating metabolising enzymes related to the regulation of adipogenesis, leading to abnormal secretion of leptin, adipokines and adiponectin and can cause alteration to the involvement of adipocytes in endocrine function (Ernst et al., 2020).

DEHP could potentially lead to endometriosis development through modifying transport, metabolism, signalling, secretion, and synthesis of hormones (Dutta et al., 2022). A study by Kim and Kim (2020) showed that exposure to phthalate esters, such as DEHP, increases resistance, proliferation, and cell viability in endometrial cells through increased oxidative stress and its ability to affect hormone receptors and inflammatory receptors (Kim and Kim, 2020).

Another EDC found to be associated with endometriosis is BPA, one of the main components of plastics for drink containers and food packaging and found in smaller

amounts within the soil and air. Therefore, human exposure to BPA is common (Wang et al., 2020).

BPAs effect on endometriosis can be seen through various mechanisms. The toxicity of BPA enables the chemical to amplify endogenous hormone estradiol (E2) which can lead to increased oxidative stress and inflammatory signals through increased estrogen sensitivity (Ruiz et al., 2021). This unbalancing of estrogen (or estrogen sensitivity) leads to estrogen acting as a carcinogen with the metabolism of estrogen leading to oxidative stress through stimulating nitric oxide synthase (White et al., 2010). This oxidative stress induces damage to hepatocytes, produces reactive oxygen species and reduces the gene expression of antioxidants which can lead to hepatoxicity (Sadasivam et al., 2022). Hepatocytes, specifically hepatocyte nuclear factor (*HNF*)-1β is responsible for invasion and proliferation stimulation in multiple cells and binding of endometriotic cells (Akasaka et al., 2013). This increased oxidative stress in the endometrium and endometrial cells leads to changes in inflammatory signalling, specifically macrophages and adipocytes increases inflammation (Cho et al., 2018). Due to the inflammatory nature of endometriosis BPA can therefore be seen as a factor of endometriosis.

Furthermore, BPA exposure may induce endometriotic phenotype for following generations and compromise ovarian function through prenatal exposure (Cho et al., 2020). As shown above BPA has potential impacts on genes and following generations. Therefore, it is possible that there is an environmental influence on a genetic susceptibility to developing endometriosis.

This section has shown that even though there is a potential genetic susceptibility to developing endometriosis there are potential environmental influences acting upon the genes involved in endometriosis.

4.4.0 5 Genes and their significant variants found to be potential factors in endometriosis onset and progression and the environments influence on these genes.

Out of the 57 notable genes of potential genomic areas of interest in relation to endometriosis found within the literature search, five were picked to investigate further which led to six significant variants to be identified. These genes and significant variants are *IDO1* (rs72643906)*, IL-6* (rs2069840, rs34880821)*, CNR1* (rs76129761)*, KISS1R* (rs933717388) and *TACR3*.

4.4.1 *IDO1* and associated significant variant as a potential factor in endometriosis onset and progression

This study found *IDO1* located on chromosome 8 (8: 39,902,275-39,928,790 forward strand) (Ensembl 2023) to have a significant variant in the endometriosis cohort, rs72643906 (seen in section 3.4). Although, there are no publications for this SNP it is a very rare variant found mostly in European populations and is highly conserved in mammals and vertebrates (UCSC, 2023). This means that this variant has potentially been conserved through selection as an evolutionary constraint such as limitations of adaptive solution, selective pressure, or natural selection (Retekska et al., 2007). Therefore, it is possible this variant has an advantageous effect due to natural selection. However, limitations of adaptive solution may have led to this variant being conserved, despite of detrimental effects within European populations. Interestingly, UCSC, (2023) research found this variant to be associated with an increased risk of COVID-19. It is possible to hypothesise that this variant is disadvantageous in relation to the immune system and endometriosis due to literature demonstrating *IDO1* can increase growth of endometriosis implants by implantation and invasion of shedding endometrium within peritoneum (Kong et al., 2021), through the enhancement of endometrial stromal cells invasion and survival within signalling pathway JNK activation (Song et al., 2016).

IDO1 is an heme enzyme located within immune system pathways and catalyses tryptophan to NFK metabolism (Tang et al., 2021). Activation of *ID01* occurs within *IDO1-KYN-AhR* signalling pathway preventing proinflammatory responses becoming extreme, however, if activated within chronic inflammation states it can become detrimental. Because suppressive signalling triggered from *PI3K p110* and Src homology region 2 domain-containing phosphatase-1 (*SHP-1)* proteins binding to two immunoreceptor tyrosine-based inhibitory motifs (*ITIM*) contained within *IDO1*. *IDO1-KYN-AhR* signalling pathway can promote immunosenescence and

suppresses effector immune cell functions, while impairing autophagy, remodelling extracellular matrixes and stimulating cellular senescence. This is through *IDO1* catabolising *L-Trp* into *NFK* following into *KYN* which stimulates the *KYN* pathway (Zhang et al., 2024), which potentially influences chronic inflammatory states of endometriosis.

rs72643906 is a downstream variant which is potentially related to interfering either transcription or translation. This may influence endometriosis prognosis through altering expression levels of *IDO1*.

Altered expression of *IDO1* has been previously researched in relation to endometriosis. Brooks et al., (2016) found *IDO1* expression is driven by increased corticosteroids and immune system activation. Specifically, interaction of corticosterone and interferon gamma *(IFN-γ)* can increase full length and variant *IDO1* expression. This increased expression can potentially influence endometriosis, due to Brooks et al., (2016) finding that suppression of matrix metalloproteinase-9 and cyclooxygenase-2 expression via the inhibition of *IDO1* can decrease invasion, proliferation, and adhesion of endometrial cells. Therefore, we can hypothesis that promotion of *IDO1* can incite matrix metalloproteinase-9 and cyclooxygenase-2 expression therefore increasing invasion, proliferation, and adhesion of endometrial cells, leading to endometriosis onset and progression. Mei et al., (2013) also supports a link between increased *IDO1* expression and endometriosis, through finding an increased expression of *IDO1* within endometrial stromal cells of endometriosis patients compared to controls. Increased expression may lead to increased survival, apoptosis, invasion, and proliferation of endometrial stromal cells.

However, studies by Tanha et al., (2022) and Napolini et al., (2019) have conflicting results when compared to the above by finding a link between decreased *IDO1* expression levels and endometriosis. Tanha et al., (2022) found endometriosis patients to have decreased levels of *IDO1* when compared to patients who did not have endometriosis, concluding that due to *IDO1*'s involvement within inflammatory response may not play a role within pathogenesis of endometriosis.

Research by Napolini et al., (2019) focusing on aspergillosis (infection of *Aspergillus* conidia fungus) found polymorphisms of *IDO1* led to a decrease in function and

expression of *IDO1*, increasing inflammatory responses when *IFN-γ* induces macrophages and inflammatory mediators such as cluster of differentiation 4 (*CD4+)* and natural killer (NK) cells to rise phagocytosis in response to *Aspergillus conidia*. Due to *IDO1* being an inflammatory suppressor and its expression in immune cells, *IDO1* can regulate homeostasis of the immune system. This decrease in function and expression of *IDO1* can unbalance *IDO1*-mediated homeostasis leading to an increased inflammatory response which has been shown in several diseases such as IBS and gastrointestinal tumours (Acovic et al., 2018). These variations in literature found is potentially due to the altered expression of *IDO1* (either increased or decreased) unbalancing *IDO1*-mediated homeostasis potentially leading to endometriosis development through either decreasing the function of *IDO1* as seen in Napolini et al., (2019) or through increased expression of *IDO1* promoting immunosenescence resulting in chronic inflammatory states seen in endometriosis.

Furthermore, UCSC research shows rs72643906 may impact upon the TF *ZIC2.* The function of *ZIC2* is as a transcriptional repressor which potentially regulates specific tissue expression (Luo et al., 2015), which is notable due to a decrease in *IDO1*'s expression and has been shown to reduce proliferation of endometrium tissue (Mei et al., 2012). Therefore, if rs72643906 impacts upon the binding site of *ZIC2* it potentially prevents the inhibition of specific pathways. Specifically, Cai et al., (2021) found decreased *ZIC2* expression levels to be associated with proliferation, invasion, and migration of endometrial cancer cells (ECC) proliferation to be inhibited. This was through *ZIC2* upregulating *lncRNA* (Long non-coding RNA) *SNHG12* (Small Nucleolar RNA Host Gene 12) expression activating the notch signalling pathway, causing migration and proliferation of ECC to increase. This was proved through finding an increased upregulated expression levels of *ZIC2* within ECC tissues and cell lines, further concluding that within ECC *ZIC2* may be an upstream mediator of *SNHG12*.

In relation to endometriosis, if rs72643906 impacts upon the binding site of *ZIC2* preventing ZIC*2* from binding, this may potentially lead to increased *ZIC2* expression levels, leading to increased proliferation, invasion, and migration of endometrial cells, and therefore, potentially endometriosis implants. This hypothesis is further

supported by Kao et al., (2003) finding *ZIC2* to be upregulated in endometriosis patients.

Exposure to BPA has been shown to decrease *ZIC2* expression via disrupting the sonic hedgehog pathway (Brown, 2009). Merrill et al., (2023) found that phenol exposure specifically BPA and TBBPA can decrease methylation of *IDO1*'s mRNA and DNA. This was found through dietary exposure to these phenols resulting in increased embryonic haemorrhaging rates within the immune maternal foetal environments resulting in decreased *IDO1* protein levels within trophoblast giant cells and methylation of *IDO1* DNA within placenta. These EDCs potentially offset the potential effects of rs72643906. This is through patients with rs72643906 mutation potentially have an increased risk of endometriosis through increased *IDO1* and *ZIC2* expression, however, when exposed to BPA this expression is decreased offsetting rs72643906 potential detrimental effect.

However, rs72643906 patients exposed to TCDD may have an increased risk of endometriosis, through TCDDs ability to increase *IDO1* expression. Tanha et al., 2022 found evidence of TCDD exposure increasing *IDO1* expression levels. Matta et al., 2021 also found a positive association of TCDD exposure and endometriosis specifically with endometriotic tissues having a concentration of TCDD which was greater in endometriosis patients when compared to controls using a systematic review.

4.4.2 *IL-6* and associated significant variants as a potential factor in endometriosis onset and progression

This study found *IL-6* located on chromosome 7 (7:22,725,884-22,732,002 forward strand) (Ensembl 2023) to have two significant variants in the endometriosis cohort these were rs2069840 (seen in section 3.8) and rs34880821 (seen in section 3.7), which were found to be referenced in previous literature, and rs34880821 was referenced in three publications. The variant rs2069840 was found to be significant in a χ^2 using frequencies but not counts.

Kim et al., (2023) referenced rs34880821 when researching genetic differences in onset age in asthma and lung function but did not find rs34880821 to be significant. Cremer et al., (2023) also found no significance for rs34880821 when studying

inherited variants in *IL-6* pathway and inflammatory activation. Li et al., (2020) also referenced rs34880821 but did not find the SNP to be significant when researching a causal relationship between type 1 diabetes mellitus and childhood asthma.

A total of eleven publications were found to reference rs2069840. Mahajan et al., (2011) studied high sensitivity C-reactive protein levels in Europeans and the influence of genetic variations in low-grade inflammation, however, rs2069840 was not found to be a significant SNP. Du et al., (2011) researched genetic components of the hypothalamic pathway effect on weight gain and dietary factors. This study found variants on or near *IL-6* to increase the risk of obesity in humans but did not find any SNPs to be significantly associated. Curtin et al., (2010) study considered rs2069840 to be associated with colorectal cancer but was not seen to be associated. Giante et al., (2010) found endothelial cells thrombin to stimulate pro-inflammatory mediators through a pro-atherogenic effect in myocardial infarction in men, however, no variants were found to be associated. Yanbaeva et al., (2009) hypothesised *IL-6* genetic variants may be associated in systematic inflammation, however, no SNPs were found to be significant. Cambarros et al., (2009) found a chronic decrease in *IL-6* expression is associated with age-related declines, through examining five different SNPs including rs2069840, but did not find significance. Both Silander et al., (2008) and Beckers et al., (2010) found a strong association between rs2069840 and cardiovascular disease in men but not in women. McCann et al., (2012) did not find rs2069840 to be significant for pain versus no pain prior to breast cancer surgery in women. Illi et al., (2012) found a significant elevation of *IL-6* and other pro-inflammatory cytokine levels in major depression patients, leading to analysis of rs2069840 in pro/anti-inflammatory cytokine genes but did not find significance. Dema et al., (2009) genotyped rs2069840 to observe association with polymorphisms and celiac disease and observed a trend in a transmission disequilibrium test but did not find it to be significant. However, rs2069840 and -174G/C had the greatest correlation of pairs, showing consequence of etiologic factors through association of two alleles in linkage disequilibrium increasing susceptibility for celiac disease. However, none of these papers were seen to investigate the variants effect in endometriosis patients.

Both significant variants (rs2069840, rs34880821) are intronic variants potentially altering the expression of *IL-6*. Altered levels of *IL-6* have been identified in endometriosis patients (Kuwan et al., 2021). Benjamin et al., (2020) found higher levels of *IL-6* in peritoneal fluid of endometriosis patients compared to controls using meta-analysis, concluding varied expression of *IL-6* influences proinflammatory-cytokine, influencing inflammatory and reproductive pathophysiology's of reproductive disorders.

The functions of *IL-6* is within inflammation and maturation of B cells pathways, with translated proteins secreted into serum at sites of chronic and acute inflammation induction (Aliyu et al., 2022). When *IL-6* is dysregulated, production of cytokine secretion in endometrial tissues rises, increasing cellular proliferation and angiogenesis within endometrium (Moghaddam et al., 2022). This causes an exacerbated immune response, increasing rate of endometrial cell shedding (Sobstyl et al., 2023). Li et al., (2016) also found an increased *IL-6* concentration within peripheral blood samples of endometriosis patients compared to controls interfering with immune and inflammatory functions, possibly promoting endometriosis pathogenesis.

The SNP rs2069840 was found to be high within Vietnamese, Korean and Estonian populations and was seen to be conserved in rhesus monkeys, mice, and dogs, but not humans (UCSC, 2023). This means rs2069840 was not conserved in humans after divergence of rhesus and human linages (Jackson et al., 2021). This is potentially the result of the SNP not being advantageous in relation to natural selection.

Whereas rs34880821 was found to be high within Vietnamese, Korean and Northern Sweden populations and was only seen to be conserved in humans but no other species (UCSC, 2023). This may mean the variant has subtle changes to a phenotype and has minimal transcript support or is a minor transcript (West et al., 2007). However, UCSC (2023) data found rs34880821 to be a Neandertal variant (Briggs et al., 2007; Green et al., 2010). Neandertal variants are variants inherited from Neanderthals which are prehistoric humans who settled in England and Western Asia. These variants were conserved through natural selection by potentially aiding in adaptations to high latitudes and seasonal light level variation

(Vernot et al., 2016). Although, Neandertal variants have also been associated with increased viral infection protection, these variants have also been shown to increase severe disease susceptibility specifically association in auto-immune/inflammatory conditions (Zhou et al., 2022). Another study found Neandertal variants may predispose increased pain sensitivity through increased sensory neuron levels (Zeberg et al., 2020).

Due to immune and inflammatory nature of endometriosis, it is possible that Neandertal variants specifically rs34880821 may increase endometriosis symptoms and implants. Specifically, *IL-6* stimulates *CD163* expression which is associated with tissue repair and T helper 2 (TH2)-type immune response. This balances humoral immune responses which occurs through B lymphocytes producing antibodies within adaptive immunity and cellular immune responses which is a primary immune response using cytotoxic T cells and macrophages to destroy infected cells and intracellular pathogens (Zhao et al., 2020). Furthermore, this pathway can lead to the inhibition of T-lymphocyte proliferation. This prevents autoimmunity where the immune system can begin to attack its own cells (Kurup and Pozun, 2022). In relation to endometriosis *IL-6* could potentially stimulate an anti-inflammatory response naturally to endometriotic lesions, however, if there are disruptions in the expression levels of *IL-6* this anti-inflammatory response may not occur. Furthermore, disruptions within this pathway may lead to disruptions within the immune system leading to the inflammation seen within endometriosis patients.

Furthermore, exposure to TCDD was found to increase *IL-6* expression levels when exposed to TCDD, when compared to no exposure (Tanha et al., 2022). With Matta et al., (2021) also finding a positive association of TCDD exposure and endometriosis. TCDD exposure can, therefore, be seen to influence endometriosis expression, specifically by increasing levels of *IL-6* expression. Therefore, it is plausible that participants with the variants rs2069840 and rs34880821 have an increased risk of endometriosis through the variants potentially increasing *IL-6* expression, however, exposure to TCDD can further exacerbate this risk through further increasing *IL-6* expression.

4.4.3 *CNR1* and associated significant variants as a potential factor in endometriosis onset and progression

This study found *CNR1* located on chromosome 6 (6:88,139,864-88,166,347 reverse strand) (Ensembl 2023) to have two significant variants in the endometriosis cohort these were rs76129761 (seen in section 3.6) and rs806372 (seen in section 3.5). Although, rs76129761 was not referenced in any previous publications, rs806372 was found within three publications. Feng et al., (2010) genotyped the *CNR1* locus in 20,000 participants with class three obesity suggesting association with increasing levels of fasting triglyceride levels. The *CNR1* gene is located on chromosomes 6 reverse strand and contains linkage disequilibrium (non-random association of alleles resulting from coinheritance and proximity within a chromosome of alleles at multiple loci) in two distinct blocks (Al-Maskri et al., 2012). The first block is located downstream of the locus confined in a single exon within a coding region. The upstream noncoding region exons is in the second block, rs806372 tags the block of linkage disequilibrium at the start site of the *CNR1* gene (Riberio and de Fatima Sonati, 2007). Yao et al., (2018) concluded personality traits within African American population is aided by *CNR1*, through results finding significant associations between psychiatric disorders and various variants within *CNR1*, through using 3,046 African American participants in an imputation-based association analysis on 26 *CNR1* variants (including rs806372). This variant was shown to have a role in the alteration of psychiatric conditions and personality with association with extraversion, agreeableness, openness, and conscientiousness after a SNP priority score analysis was produced. Navarro et al., (2022) found that rs806372 is associated with extraversion through conducting a literature review and translational approach to investigating molecular alterations in psychiatric disorders related to ECS.

rs806372 was found to have a potential splicing site (see table 26) which potentially alters transcription or translation of *CNR1* through creating alternative splicing potentially creating alternative haplotype sequence alignments of *CNR1*. This means this is a potentially causative SNP through altering the representation of a locus, and rs76129761 is a deleterious intron (CTCT changing to CT) and may also influence endometriosis prognosis through altering expression levels of *CNR1*. This is because *CNR1* encodes one cannabinoid receptor of two and is part of the family of guanine-nucleotide-binding protein (G-protein) coupled receptors and is involved in the ECS (Lu and Potter, 2017). Cannabinoid receptors are within the GPCR family and act as intercellular lipid messengers working as signalling molecules which

activate cannabinoid receptors from one cell to another (Zou et al., 2018). Immune cells and inflammatory factors directly influence inflammation of tissues affected by ECS as they change behaviour and production of immune cells (Rahaman and Ganguly, 2021), acquiring qualities of anti-proliferative, anti-nociceptive and anti-inflammatory (Lingegowda et al., 2022). Therefore, ECS may influence aetiology and pathophysiology of endometriosis through involvement within inflammation and immune pathways.

Specifically, literature suggests *CNR1* may be involved in aetiology of endometriosis through intense expression within endometriotic lesions (Allam et al., 2022). Bouaziz et al., (2017) showed *CNR1* has increased expression within the immune system and uterus while having a role within female reproduction with *CNR1* expression varying throughout the menstrual cycle. Allam et al., (2022) also found significantly higher expression and a change in pattern of *CNR1* expression in ovarian endometriotic lesions compared to controls, using gene expression assays, concluding endometriosis-associated immune response and chronic pain is mediated by *CNR1*. An increased expression in CNR1 has also been seen in endometrial cancer patients. Ding et al., (2021) found an association with endometrial cancer and resistance of progesterone and *CNR1* expression. This is because a decrease in *CNR1* expression down-regulated extracellular signal-regulated kinases (ERKs) expression. Furthermore, an increase in *CNR1* expression was shown in progesterone resistant cells within endometrial cancer patients. When *CNR1* expression was decreased migration and proliferation of the progesterone resistant cells was also decreased. Therefore, it is possible changing expression levels within *CNR1* may lead to endometriosis onset and progression through stimulating apoptosis, inhibiting decidualisation and increasing migration and proliferation of cells.

However, there is conflicting data with Tanaka et al., (2022) finding lower levels of *CNR1* within endometriosis patients' endometrial tissues when compared to healthy controls independent of menstrual cycle phase. This was concluded through endocannabinoids being present in endometrium tissue and may stimulate apoptosis and inhibit decidualisation of endometrium tissue.

The rs76129761variant is high within Northern Sweden, Estonian, and Korean populations and is highly conserved in humans, rhesus monkeys, mice, and dogs (UCSC, 2023). This means that this variant has potentially been conserved through selection as an evolutionary constraint, therefore, it is possible this variant has been conserved through having an advantageous affect, irrespectively it may have been conserved despite detrimental effects due to limitations of adaptive solution or may be detrimental through environmental pollutants. For example, Forner-Piquer et al., (2018) found exposure to DiNP and BPA caused disruption of the ECS in the gonadal of zebrafish. Because exposure to DiNP and BPA significantly increased the expression of *CNR1*. Therefore, rs76129761 may have been conserved as an adaptive solution, however, when patients with this variant are exposed to environmental pollutants such as BPA an DiNP, there is the potential for endometriosis risk through increased *CNR1* expression.

Furthermore, UCSC (2023) found rs806372 to be a Denisovan variant, making the variant more prevalent in east Asian populations (UCSC, 2023; Reich et al., 2019; Meyer et al., 2012). A Denisovan variant is a variant inherited from Denisovans which are prehistoric humans who settled in Asia, these variants tend to have a part in immune responses or high-altitude adaptions and therefore, may have been conserved due to natural selection (Vernot et al., 2016). However, Denisovan variants may also impact upon the probability of disease development. Asian women have a high prevalence of endometriosis at 15.4%, compared to European populations (1.4%) and the general population (4.44%) (Parazzini et al., 2020). Therefore, this variant may increase the risk of endometriosis in Asian populations, which may have spread overtime without endometriosis prevalence. However, exposure to pollution may have increased the risk of endometriosis onset. Specifically, EDCs such as DEHP, DiNP and BPA, may have increased the likelihood of endometriosis through altering the expression of *CNR1*. Specifically, when patients with rs806372 are exposed to DEHP, they may have an increased risk of endometriosis. Because, DEHP (seen in section 4.3) has a direct influence on the ECS. DEHPs ability to upregulate metabolising enzymes related to ECS such as *CNR1* during adipogenesis causes secretion of leptin, adipokines and adiponectin, causing alteration to adipocytes involvement in endocrine function (Ernst et al., 2020). Alteration of ECS leads to endometriosis through un-regulating inflammatory

and pain processes from ECS manifold immunomodulatory effects from bioactive lipids (Barrie and Manolios, 2017).

UCSC (2023) data has also shown rs76129761 lies on various TF binding sites, these are *ZNF701*, *SOX4*, *SOX6*, *FOXD3*, and *SOX11*.

Limited literature could be found on *ZNF701*, specifically in relation to endometriosis, endometrium, cancers, or EDCs. However, *ZNF701*'s predicted involvement is within transcription regulation by RNA polymerase II, transcriptional regulation, enabling the activity of DNA-binding transcription factor and is potentially active within the nucleus (Dimond et al., 2024). This TF is a protein coding gene related to nucleic binding and is located within pathways of gene expression and transcription. Due to the menstrual cycle influencing gene expression, specifically genes related to steroid hormones within the endometrium, it is possible altered transcription and regulation of gene expression levels may be a potential genetic risk factor of endometriosis (Fung et al., 2018). Therefore, it can be hypothesised that rs76129761 may inhibit *ZNF701* from binding increasing its expression levels, leading to increased activity of DNA-binding transcription factor, causing alteration of gene expression within the endometrium, leading to endometriosis.

SOX4 functions within apoptosis pathways and can cause tumorigenesis or cell death. This is due to involvement within cell fate regulation and may act as a regulator of transcription (Vervoort et al., 2013). Moreno, (2020) found *SOX4* promotes migration, metastasis, cell survival, and epithelial to mesenchymal transition. When *SOX4* expression is decreased cancer cell migration and regulation of epithelial to mesenchymal transition (this is seen as a required step of solid tumour metastasis) is also decreased. This is where epithelial cells loose cell adhesion and polarity but acquire properties of invasion and migration to become mesenchymal stem cells which are stromal cells having multilineage differentiation and can self-renew, which may be segregated from tissues such as menstrual blood and endometrial polyps. When *SOX4* expression is decreased it also reduces cancer cell migration. Therefore, it is possible that increased *SOX4* expression may promote endometriosis implants and lesions through increased regulation of epithelial to mesenchymal transition and promotion of migration, metastasis, and cell survival. Furthermore, Al-Deresawi et al., (2018) found an association between malignancy

(cervical and endometrial cancer) and *SOX4* expression. Specifically, *SOX4* expression was increased within endometrial adenocarcinoma patients. Zhao et al., (2019) also found *SOX4* to be upregulated in tissues and cell lines of endometrial carcinomas. However, Huang et al., (2022) found *SOX4* to regulate decidualization of human endometrial stromal cells and repress E2 to modulate the stability of progesterone receptors and is seen to be downregulated in endometriosis patient's endometrium. It is possible that the upregulation of *SOX4* by exposure to BPA (Kang et al., 2014) may increase promotion of endometriosis implants and lesions through increased regulation of epithelial to mesenchymal transition and promotion of migration, metastasis, and cell survival.

SOX6 can interact with other *SOX* TF to activate gene expression (Liu and Lefebvre, 2015), therefore, alterations to this TF may increase the expression levels of *CNR1*. Zhang et al., (2015) found *SOX6* to potentially aid in endometriosis progression through cell invasion, metastasis, and proliferation. Specifically, decreased *SOX6* expression levels were seen in ectopic endometrial tissues when compared to controls. Furthermore, Pu et al., (2017) found exposure to BPA caused *SOX6* to diverge in preadipocytes, and Lichtensteiger et al., (2021) found BPA and PCB (polychlorinated biphenyl) exposure led to upregulation of *SOX6*. Therefore, it is possible for decreased expression of *SOX6* to lead to cell invasion, metastasis, and proliferation of endometrial cells, however, due to BPA and PCB upregulating *SOX6* this may counteract the effect.

FOXD3 is involved in protein coding, transcriptional regulation of pluripotent stem cells and embryonic stem cell (ESC) pluripotency and is also associated with autoimmune diseases (Cassar and Stanford, 2012). Mathew et al., (2016) found that *FOXD3* is expressed differently in endometriosis patients but is dynamically expressed within controls endometrium. Specifically increased expression of *FOXD3* and mRNA levels in endometrial cells were seen in untreated endometriosis patients, where *FOXD3* moved from the nucleus to the cytoplasm. The study found when *FOXD3* expression is decreased endometriosis was reduced. Baba et al., 2009 found a decrease in *FOXD3* expression when exposed to BPA, reducing disruption and differentiation of notch signalling (regulation of cell-fate) and supressing *FOXD3* expression. Therefore, upregulation of *FOXD3* expression may promote endometrial

implants. However, BPA may mitigate against this by downregulating expression of *FOXD3*.

SOX11 is involved in cell fate determination and regulating embryonic development (Kamachi et al., 2013). Tsang et al., (2020) found that *SOX11* is potentially a mediator of pro-inflammatory cytokines through activation of developmental pathways by activation of core embryonic programs in adult epidermal tissues leading to enhanced migration, remodelling of extracellular matrix and cell proliferation. This may explain Shan et al., (2019) and Chang et al., (2017) findings of increased *SOX11* expression within endometrial ECC lines when compared to controls. Wasik et al., (2014) found a positive correlation between increased expression levels of both *CNR1* and *SOX11*. Similar to *SOX6* Lichtensteiger et al., (2021) found exposure to PCB and BPA increased *SOX11* expression. Due to this information, it can be hypothesised that increased levels of *SOX11* can also increase expression of *CNR1* while also enhancing migration and proliferation of endometriotic cells, which is further enhanced through exposure to PCB and BPA.

UCSC (2023) data has also shown that rs806372 lies upon the binding start site of the TF *SOX12*. *SOX12* functions in fate decisions of cells within a range development processes (proliferation and metastasis). The TFs expression in various tissues (endometrium, ovary, cervix, breast, and endocrine), implies functions in maintenance and differentiation in a diverse range of cells, specifically mesothelial cells (specialised epithelial cells), mitotic cells (undifferentiated cells), pluripotent stem cells and endocrine cells (Schock and LaBonne, 2020). Due to *SOX12* expression in endocrine and female reproductive tissues, it may be hypothesised that *SOX12* may affect the cell fate decisions of endometrial cells (proliferation and metastasis of endometrial cells for example), therefore, potentially leading to endometriotic lesions. This is further validated by Qu et al., (2018) finding upregulation of *SOX12* stimulates migration and invasion of tumour cells, when investigating breast cancer cells. DEHP can further increase *SOX12* expression levels through causing changes in DNA methylation leading to oxidative DNA lesions from cell death (Chou et al., 2019).

4.4.4 *KISS1R* and associated significant variant as a potential factor in endometriosis onset and progression

This study found *KISS1R* located on chromosome 19 (19:917,287-921,005 forward strand) (Ensembl 2023) to have a significant variant in the endometriosis cohort. This was rs933717388 (seen in section 3.9) and is a potentially novel variant as there are no publications or records on genome-wide association studies (GWAS) central or SNPedia referencing this variant. However, rs933717388 is seen to be conserved in humans but no other species (UCSC, 2023). This may mean the variant has subtle changes to a phenotype and has minimal transcript support or is a minor transcript (West et al., 2007).

Due to rs933717388 being an intronic variant, which potentially alters the expression of *KISS1R,* which hypothetically leads to endometriosis progression through promoting metastasis and disruption to reproduction regulation. This is because, *KISS1R* can supress metastasis of breast carcinomas and melanomas in humans without tumorigenicity affected. This means that it is possible for altering expression or variants within *KISS1R* to lead to endometriosis through increased metastasis of endometriotic cells outside of the uterus leading to endometrial implants and lesions (Gillespie et al., 2022). *KISS1R* also impacts follicular development, oocyte maturation, ovulation, and steroidogenesis (Hu et al., 2018). Blasco et al., 2020 showed women with endometriosis had a significantly higher *KISS1R* expression and had abnormal expression within granulosa cells when in comparison to healthy women, concluding *KISS1R* role within the HPGA and reproduction regulation, and may be a factor within the onset of endometriosis.

UCSC (2023) data has shown rs933717388 lies on TF's *ZNF707* and *ZBTB11* binding sites. Limited literature could be found on *ZNF707*, specifically in relation to EDCs. *ZNF707* predicted involvement is within transcription regulation by RNA polymerase II, transcriptional regulation, enabling the activity of DNA-binding transcription factor and is potentially active within the nucleus, and is associated with ovarian clear cell adenocarcinoma (Ov-CAA) (Khowal et al., 2021). A study by Kim et al., (2020) found *ZNF707* to have a functional role in tumorigenesis and Ov-CAA associated with endometriosis, through endometriosis causing an increased risk of Ov-CAA and in ovarian endometrioma *ZNF707* is hypermethylated when compared to eutopic endometrium. This study found *ZNF707* expression levels to be increased in epithelial ovarian carcinoma when compared to controls of ovarian surface

epithelial cells and an increase in *ZNF707* expression also increased the risk of Ov-CAA.

There was also limited literature found on *ZBTB11* and EDCs, however, like *ZNF707, ZBTB11* predicted involvement is within transcription regulation by RNA polymerase II, transcriptional regulation, enabling the activity of DNA-binding transcription factor and is potentially active within the nucleus (Xu et al., 2024). Qin et al., (2021) found an association between elevated *ZTBT11* expression levels and epithelial ovarian cancer.

A higher expression of *KISS1R,* potentially via rs933717388, may lead to endometriosis through increased metastasis of endometriotic cells outside of the uterus leading to endometrial implants and lesions and dysregulation of HPGA and reproduction regulation. The upregulation of *ZNF707* and *ZBTB11* by rs933717388 potentially preventing binding of these TF, can potentially increase transcription and tumorigenesis of endometrial cells. Therefore, it can be hypothesized that rs933717388 may be a genetic predisposing factor of endometriosis, with DEHP increasing this further by increasing *KISS1R* expression and unbalancing FSH secretion in-turn altering sex hormone functions.

Furthermore, EDCs can increase *KISS1R* expression further. Specifically, DEHP exposure influences regulators of HPGA by regulating GnRH (Gonadotropin hormone-releasing hormone) release altering *KISS1R* expression (Xie et al., 2022). Literature shows DEHP alters levels of reproductive hormones after exposure, specifically higher levels of FSHR serum and in turn *KISS1R*, through DEHP influencing the positive feedback of the GnRH pathway from pituitary release. This unbalances FSH secretion altering sex hormone function and secretion downstream pathways through the disruption of the HPGA (Graceli et al., 2020). Therefore, a participant with rs933717388 may be at a higher risk of endometriosis when compared to participants without this variant. However, this risk can be further increased when exposed to DEHP through the EDCs ability to increase *KISS1R* expression.

4.4.5 *TACR3* as a potential factor in endometriosis onset and progression

Although this study did not find any significant variants for *TACR3* located on chromosome 4 (4: 103,586,031-103,719,985 reverse strand) (Ensembl 2023), SNVs and INDELs found in *TACR3* were most prominent in endometriosis patients diagnosed with stages 2 and 3 and highlighted in stages 1 and 4 endometriosis patients (see appendices 4-10). The data found variants rs796412104 and rs565747925 to be consistent in the cohort in comparison to the GE population.

TACR3 serves as a receptor for tachykinins with association in; immune, hormonal, Class A/1 (Rhodopsin-like receptors) and GPCR downstream signalling pathways (Hendrikse, 2014). *TACR3* is also associated with HPGA regulating release of *GnRH* (Casteel and Singh, 2020). *TACR3* encodes tachykinin neurokinin 3 (neurokinin B) receptors through G protein reactions with 7 hydrophobic transmembrane regions with receptor affinities of *TACR3* with specific 5'-end of the sequence variations (Sparling, 2016).

TACR3 aids in regulating adhesion, signal transduction, dynamics of the actin cytoskeleton, vesicle trafficking and motility (Verma et al., 2024). This occurs through activating cellular reaction through mobilising Ca(2+) in reaction to a stimulus via maintaining a low cytoplasmic Ca(2+) concentration (Joseph et al., 2014). Due to *TACR3*'s involvement within the abovementioned pathway, it can be assumed that altering levels of *TACR3* may lead to increased adhesion, potentially within endometriotic cells outside the uterus leading to endometriosis implants and lesions.

Blasco et al., 2020 found lower expression levels of *TACR3* granulosa cells of endometriosis patients. Therefore, concluding altered expression within *TACR3* in granulosa cell systems may be associated with endometriosis and endometriosis associated infertility.

Similarly to *KISS1R,* DEHP exposure influences regulators of HPGA by regulating GnRH release altering *TACR3* (Xie et al., 2022).

Through the results found within this paper and the literature above *TACR3* may influence endometriosis onset and progression through increased expression levels promoting adhesion of endometriotic lesions. Exposure to DEHP may further increase these lesions through upregulating *TACR3* expression.

4.5 Concluding on identifying new biomarkers for diagnosing endometriosis effectively in earlier stages.

Genetic-based biomarkers are biological markers used within medicine usually from blood tests as an indicator of biological states (Khailany et al., 2020). These can show potential risks of developing a certain disease within asymptomatic family members at risk (Taylor et al., 2020). These can be used for diagnosing, monitoring and susceptibility of a condition or disease (Aronson and Ferner, 2017). Previous evidence suggests that if close family members have endometriosis, the patient is ten times more likely to develop it potentially due to heritability factors such as genetic variations (Laganà et al., 2019). This means that there are possible genetic factors which predispose development of endometriosis which can be screened through using genetic-based biomarkers. However, currently ESHRE guidelines do not advise using diagnostic biomarkers for endometriosis. Developing effective new biomarkers for diagnosis of endometriosis in earlier stages, would allow patients with family members diagnosed with endometriosis to be tested for genetic factors of developing the disease. If found, it is possible for the patient to be placed on preventive treatment such as the progesterone only pill to help prevent endometriotic lesions from occurring and would enable quicker and less invasive methods of diagnosis compared to the current forms (seen in section 1.3).

It is possible for the significant regulatory sequence variants found in this study to be used as potential biomarkers for diagnosing endometriosis, due to their high frequencies in this study cohort of endometriosis participants and a low frequency in the general population. Furthermore, theses variants have been shown in genes known to influence endometriosis onset and progression.

However, further studies should be conducted to determine their prevalence and accuracy when diagnosing endometriosis. Studies should include a larger number of cohorts and their family members for cascade genetic testing. A RT-PCR (reverse-transcription polymerase chain reaction) is a cost-effective and time efficient way of determining expression of variants with controls and endometriosis patients. Furthermore, functional RNA analysis of the variants can help to determine the variant functions. These processes would enable determination of whether these

SNPs are pathogenicity supported, and possible use as diagnostic biomarkers of endometriosis.

Although, biomarkers have the potential to determine at risk family members who are asymptomatic, biomarkers are unable to determine disease progression, severity of symptoms and if the patient will have symptoms at all (Ponti et al., 2020). Furthermore, as endometriosis is a multifactorial disease there may be environmental factors and multiple genetic factors which are interlinked, meaning that biomarkers may not determine the disease onset and progression.

5.0 Concluding remarks

The purpose of this study was to carry out detailed investigation into potential genes and their variants regulatory sequences causing endometriosis and how the environment may impact upon these. This study is important due to the limited knowledge on the aetiology and pathophysiology of this disease (Saunders and Horne, 2021). Even though endometriosis affects approximately 10% of reproductive age women globally (Kanellopoulos et al., 2022) it can take up to eleven years to diagnose after symptoms appear (Agarwal et al., 2019). Due to limited knowledge on this condition the aim of this project was to carry out a detailed investigation of genetic factors and their interactions with the environment (e.g. EDCs) which potentially predispose an individual to endometriosis development with subsequent objectives being:

1. To identify variants capable of predicting endometriosis development.
2. To investigate the way that environmental factors influence the identified genes and their variants and identify intersecting pathways involved in endometriosis development.
3. To predict the possibility of identified variants acting as novel therapeutic targets.

This was possible through using GE 100,000 genome project and a literature search.

The first objective was to identify variants capable of predicting endometriosis development and the third objective was to predict the possibility of identified variants acting as novel therapeutic targets. To identify this a literature search was

conducted to identify genes which were linked to endometriosis and GE 100,000 genome project was used to find potential variants within the 5 genes which were selected. The 5 selected genes were *CNR1, IL-6, IDO1, KISS1R* and *TACR3*. With subsequent variants of C*NR1 (*rs76129761, rs806372*), IL6 (*rs2069840, rs34880821*), IDO1 (*rs377490563, rs72643906*), KISSR1(*rs548130449, rs933717388*)* and *TACR3* (rs796412104, rs565747925). Six of these were statistically significant rs76129761, rs806372, rs2069840, rs34880821, rs72643906 and rs933717388 although, all variants did not have evidence of functions or gene modification, it is possible through the literature provided to suggest that these variants could predict early endometriosis development.

The second objective was to investigate the way that environmental factors influence the identified genes and their variants and identify intersecting pathways involved in endometriosis development. This required literature searches into genes found to influence endometriosis and how environmental factors influence the genes and associated pathways. EDCs were found to directly influence endometriosis development through disrupting hormone signalling, secretion, and metabolism by altering endocrine functions and either altering or mimicking hormone functions (Darbre, 2022). Each of the 5 genes shown to potentially influence susceptibility and progression of endometriosis were impacted upon by EDCs, either on the gene itself or associated pathways in which the genes are involved.

This paper showed endometriosis is hormone dependent, and that there is possible genetic predisposition towards the developing endometriosis in certain families. Exuberated pathways such as the inflammatory and immune pathways, and hormonal imbalance of estrogen dominance play a large role in endometriosis development, while dysregulation of patterns within tissue-specific arrangement of gene expression can lead to endometriosis in specific tissues, specifically ovarian endometriosis. Furthermore, exposure to pollutants can directly impact upon many of the mechanisms within the body. This has been shown by EDCs impact on endometriosis within this paper. This potentially means endometriosis is a multifactorial condition, resulting from numerous genetic and environmental factors causing dysregulation of or exuberated pathways involved in various tissues. This objective has been achieved due to the results from this study, and the findings from

other studies have enabled a better understanding of mechanisms leading to an increased risk of developing endometriosis.

The aim of the study was to carry out a detailed investigation of genetic factors that could predispose an individual to develop endometriosis, and their interactions with the environment. The aim was achieved through using the GE 100,000 genome project data and a literature search. This study found that genetic factors can increase the risk of endometriosis which may be influenced by the environment. The implications of this are that knowing genetic variants associated with endometriosis may aid in a shorter diagnosis time through using biomarkers and may enable a better understanding of endometriosis.

5.1 Limitations and further research

The study conducted has several limitations which could affect the validity of conclusions produced, and therefore, require further research. Firstly, the stage of endometriosis for each of the patients was not stated. Although the patients within this cohort had estimated stages using the clinical information provided, it is possible the stages given for each participant may not have been accurate. Moving forward, further research should include the diagnosis of endometriosis stage to accurately conclude on identifying gene/ polymorphism variants in early endometriosis development.

The second limitation was the size of the cohort and limited number of patients under the age of 29 years. This has limited the viability of the study, due to low statistical power. When repeating this study, a larger sample size should be used with the same number of patients within the age groups. This enables a better representation of the population and increase the accuracy of the research.

Furthermore, including family members of the patients to the cohort would enable cascade genetic testing and enable a determination to the heritability of endometriosis. Cascade genetic testing should be conducted for all biomarkers found, alongside RT-PCR to determine the viability of using biomarkers to diagnose endometriosis. Cascade genetic testing requires larger sample sizes including genetic information from family members to confidently conclude on the accuracy of biomarkers found to diagnose endometriosis.

Finally, further studies should include samples taken from the participant cohort. By taking samples from varying tissues, it may be possible to determine whether certain variants predispose an individual to endometriosis in specific locations.

Additionally, genome project data from other countries could also improve viability.

6.0 Reference list

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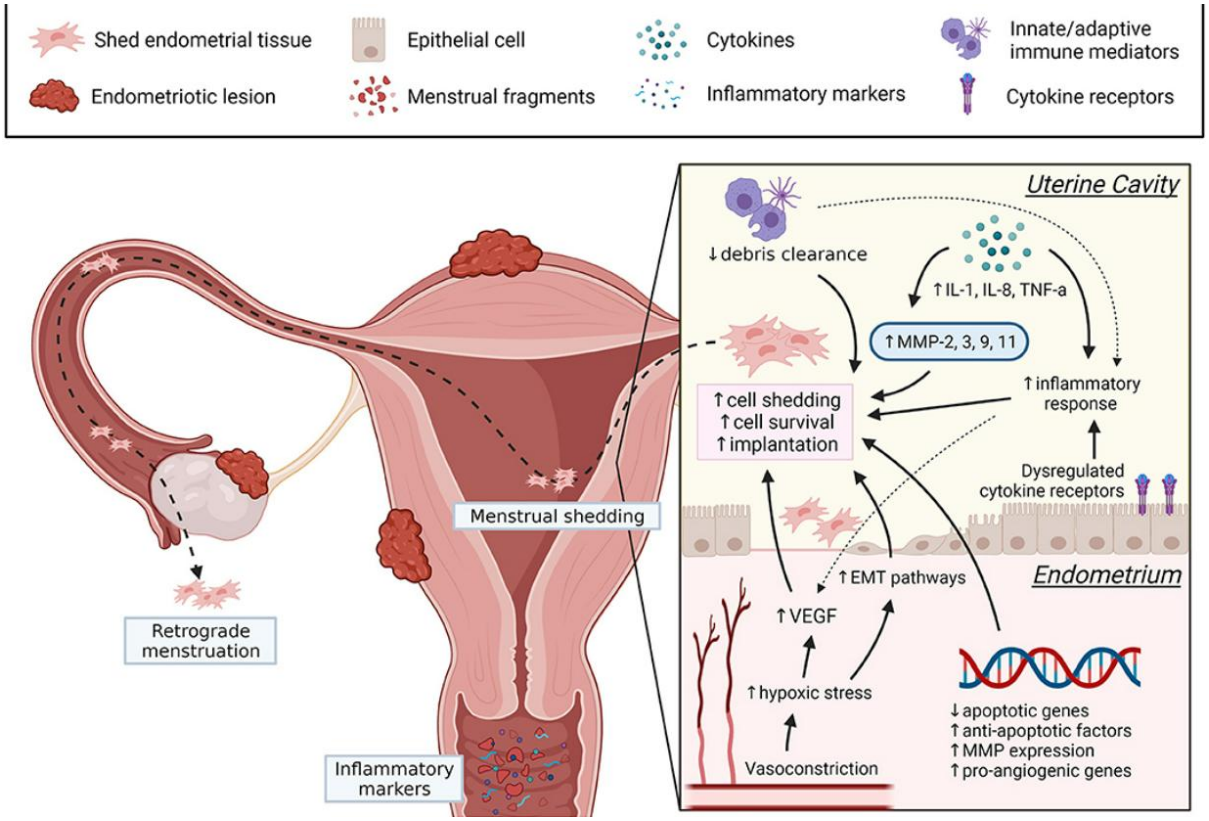
7.0 Appendix

Appendix 1: Hypotheses of endometriosis aetiology and pathophysiology

There are several hypotheses regarding the mechanism of endometrial cell implantation outside the uterus (Murgia et al., 2021). The pathogenesis of endometriosis has so far remained somewhat unclear. Endocrine and immunologic mechanisms are thought to be involved, (Marian et al., 2020), while a recent investigation suggested a pathogenic role for Fusobacterium in development of ovarian endometriosis (Muraoka et al., 2023). Pathogenic processes associated with endometriosis are metaplasia (replacement of a differentiated mature cell type for another), implantation of endometrial cells outside of the uterine cavity, and metastasis (spread of endometrial cells into another area of the body) (Lagana et al., 2019).

Xia and Yu (2022) hypothesised that endometrial tissue located outside the uterus is Mullerian in origin i.e., true endometrial tissue and comes from tubal and uterine mucosa. Another possibility is the tissue has a pseudo-endometrial origin and is derived either through metaplasia within peritoneal serosa (abdominal cavity membrane lining) or from remnants of the wolffian body (mesonephric duct which is developed in early embryonic stages) (Yovich, 2020).

Among the endometriosis-pathogenesis theories, retrograde menstruation is most likely to lead to endometriosis. Sampson first described this theory in 1925 stating that endometrial tissue can potentially ‘escape’ through fallopian tubes leading to ovarian endometriosis (reviewed in Yovich et al., 2020). This occurs through menstruation blood flowing back reaching the abdomen rather than exiting through the vagina. This theory can explain how the endometrial tissue fragments and implants on the pelvic peritoneal tissues and is contained within ovarian inclusion cysts (appendix 1b) (Smolarz et al., 2021).



Appendix 1b: From Kuan et al., (2021). The concept of retrograde menstruation (the backwards flow of menstrual blood into the uterine cavity through the fallopian tube) is shown. Vasoconstriction which increases hypoxic stress also influences the implantation of endometriosis through dysregulated cytokine receptors.

Although, retrograde menstruation is poorly understood (Persoons et al., 2020), there are published studies regarding physiological processes which enable endometrial implantation after dysregulated menstruation (Critchley et al. 2020) (Prasnikar et al., 2020). Dysregulation of inflammatory mediators, such as cytokines (*IL-6* and *IL-8*) have been identified in endometriosis patients (Kuwan et al., 2021). These increase production of cytokine secretion in endometrial tissues, increasing cellular proliferation and angiogenesis within the endometrium (Moghaddam et al., 2022). This increases the rate of endometrial cell shedding and exacerbates immune response (Sobstyl et al., 2023). Typically, matrix metalloproteinases (MMPs) mediate extracellular remodelling and endometrial breakdown during menstruation (Gnecco et al., 2023), although, mutations within the MMPs are associated with the formation of endometrial ectopic lesions (Kuan et al., 2021) through surplus of angiogenic factors in ectopic lesions, endometrial invasion, and endometrial tissues migration

(Kuan et al., 2021). However, this hypothesis is unable to explain thoracic endometriosis, which is the most prevalent site of extra abdominopelvic endometriosis is seen in 50-84% of endometriosis cases (Nezhat et al., 2019; Ogunkoya et al., 2022).

The benign metastasis theory of endometriosis was proposed in 1924 by Halban through inducing endometriosis in baboons describing mechanisms of endometrial tissue outside the uterus (reviewed in Khan et al., 2021 and Spyrou, 2022). Observations of increased levels of endometrial stromal cells in lymph nodes of baboons with endometriosis compared to controls, considered lymphatic and vascular systems are responsible for spreading the endometriotic cells to areas distant from common sites (reviewed in Mahalpure et al., 2022). Halban's theory could explain thoracic lesions associated with endometriosis (Rahmawati et al., 2018) but fails to describe endometrial lesions influence through gravitational movement in organs located closer to the uterus, such as the ovaries and the fallopian tubes, (Tony et al., 2022).

It has also been theorised that endometriosis originates from foetal cells such as Mullerian remnants, peritoneum, bone marrow or endometrial basal layer stem cells, which can either be Mullerian or non-Mullerian (Lagana et al., 2019). During foetal development the upper part of the vagina, uterus and fallopian tubes grow from a pair of tubes known as Mullerian ducts (Cunha et al., 2018). Abnormal differentiation, or relocation due to mutations in anti-Mullerian hormone (AMH) receptors, or a lack of AMH (Venkata et al., 2022) can spread primordial endometrial cells within Müllerian duct migratory pathways across the posterior pelvic floor (Signorile et al., 2022). At puberty, these cells can undergo proliferation and differentiation, under estrogens influence, causing development of endometrial tissue implants scattered within the anterior cul-de-sac (between uterus and bladder), posterior cul-de-sac (between rectum and uterus) and uterosacral ligaments (connective tissues supporting the uterus) (Klemmt and Starzinski-Powitz 2018; Rungsiwiwut et al., 2021; Lagana and Naem, 2022). However, this hypothesis cannot explain endometriotic implants within the ovary, appendix, or sigmoid colon (Yovich, 2020).

It has also been proposed that endometriosis develops through stem-cell differentiation (stem cell theory) (Maruyama, 2022). Stem cells are undifferentiated

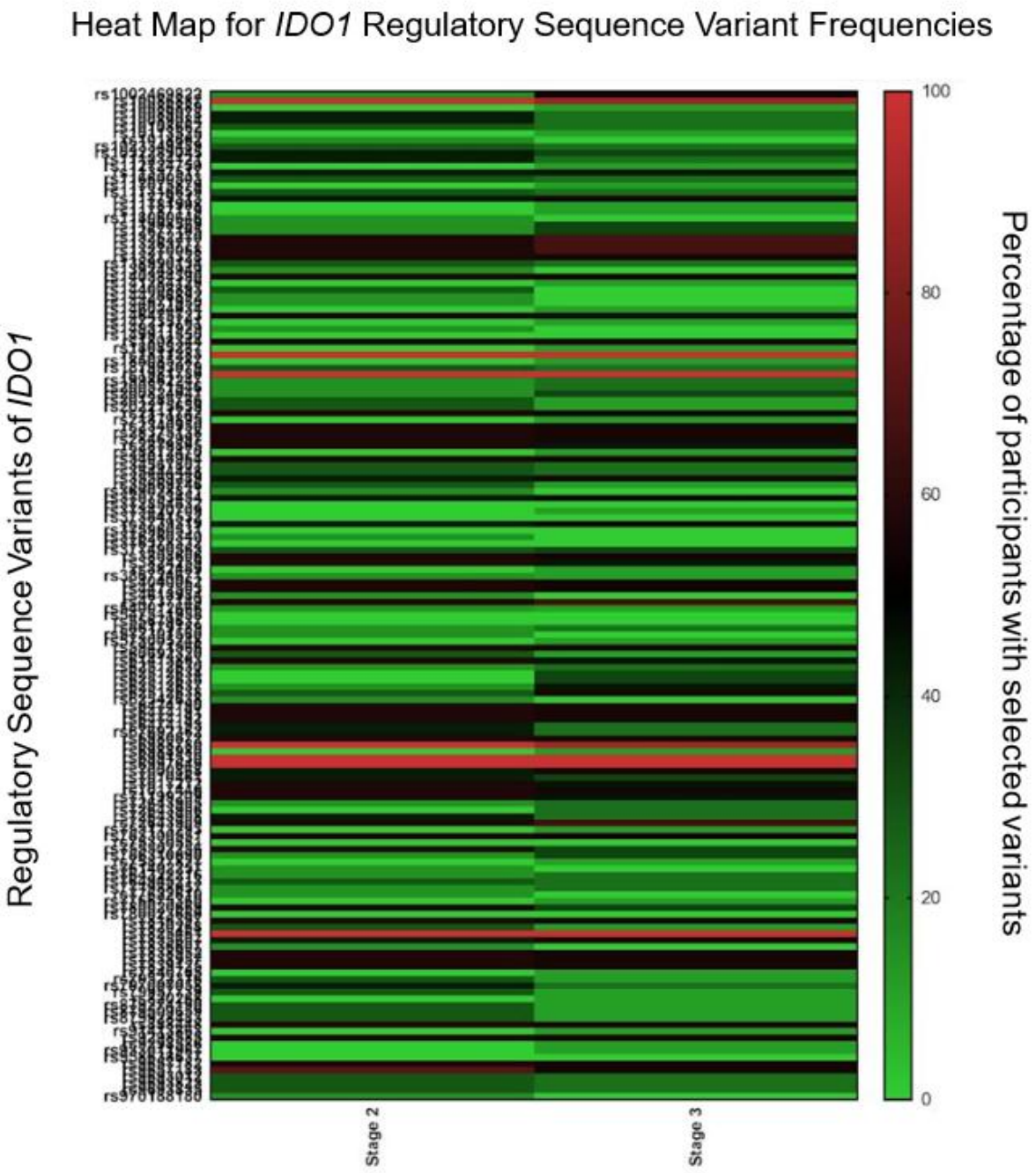
cells capable of self-renewal and differentiation to various daughter cell types (Chen et al., 2022). There are two alternative theories to describe the pathogenesis of endometriosis based on the stem cell tissue origin (Signorile et al., 2022). The first hypothesises that stem cells arise from the uterine endometrium, whereas the second postulates that stem cells originate in bone marrow (Wang et al., 2020). Irrespective of their origin, these stem cells are thought to differentiate to endometrial cells under the influence of hormones and other molecular factors (Signorile et al., 2022). Studies on menstrual blood and endometrial tissues biopsied from endometriosis patients have identified endometrial origin stromal stem cells (Cordeiro et al., 2022; Tempest et al., 2018). These observations led to the hypothesis that endometrial stromal stem cells implant on organs outside the uterus via the action of retrograde menstruation, with their subsequent differentiation to endometrial tissue (Signorile et al., 2022).

The alternative bone marrow theory hypothesises that bone marrow stem cells are misplaced in soft tissue rather than the endometrium, leading to development of endometriosis (Signorile et al., 2022). This theory has been supported by experimental data (Figueira et al., 2011; Du and Taylor 2007), and could explain the presence of endometrial tissue on organs outside the pelvic cavity.

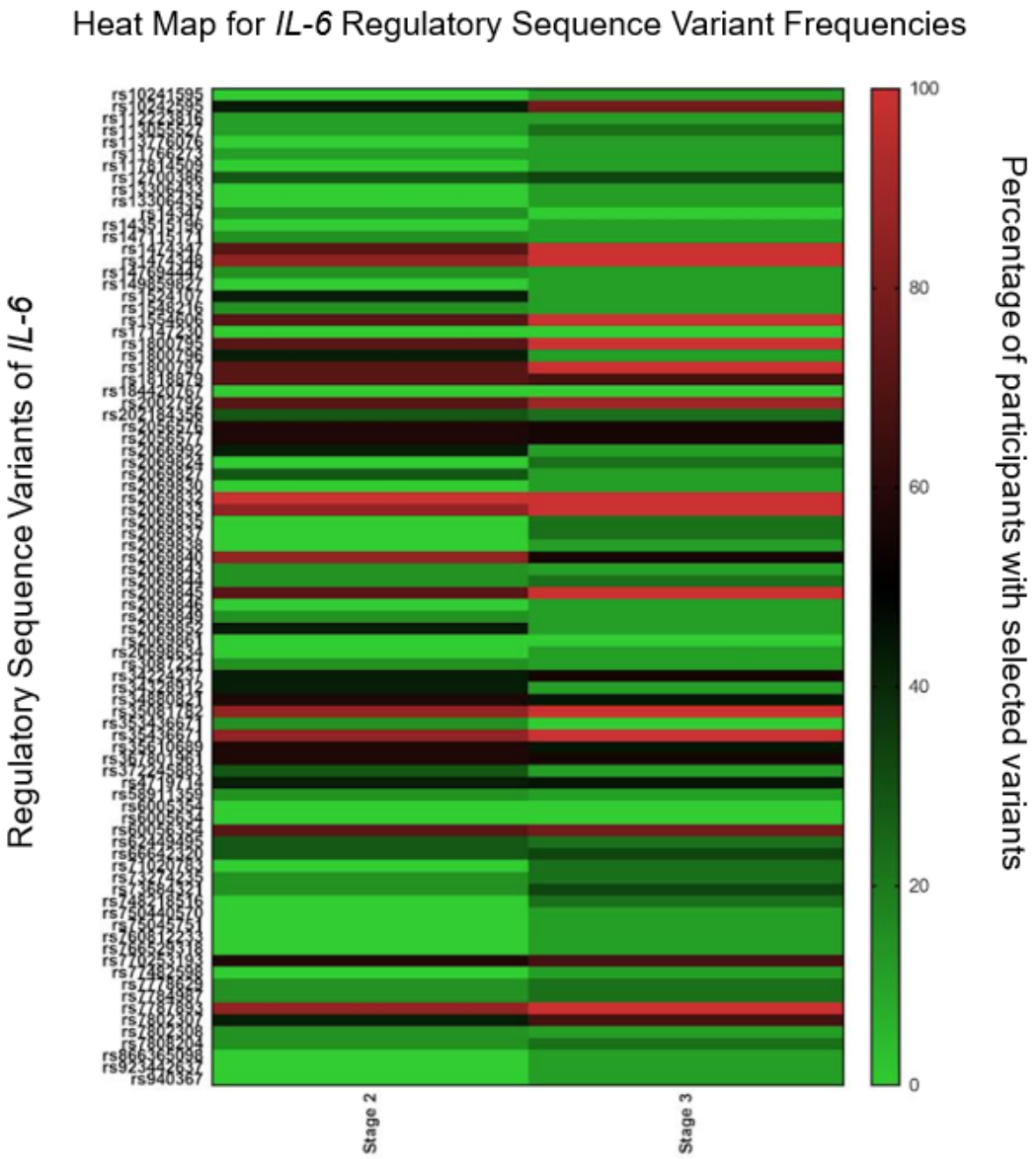
A recent investigation suggested a pathogenic role of bacterium *Fusobacterium* in developing ovarian endometriosis (Muraoka et al., 2023). *Fusobacterium* species have been described in oral and gut microbiome while *Fusobacterium nucleatum* has been shown to cause cases of vaginal dysbiosis. The study compared endometrial implants removed from the ovaries of women with endometriosis with endometrial tissue obtained from the uterus of a control group of endometriosis patients. In this study 64% of ovarian endometriotic tissues were seen to have *Fusobacterium* infiltration, while infiltration was evident in <10% of control endometrial tissue. Further biochemical and immunological experiments revealed that in women with endometriosis, a *Fusobacterium* infection leads to transforming growth factor–β (TGF-β) activation of endometrial cells. This activation gave them the ability to become proliferative, migrate and adhere in in vitro models. Mouse experiments confirmed the in vitro observations, suggesting that a proportion of endometriosis cases could be due to *Fusobacterium* infection (Muraoka et al., 2023). Importantly,

administration of antibiotics to thPe endometriosis mouse model led to significant improvement of endometriosis (Muraoka et al., 2023).

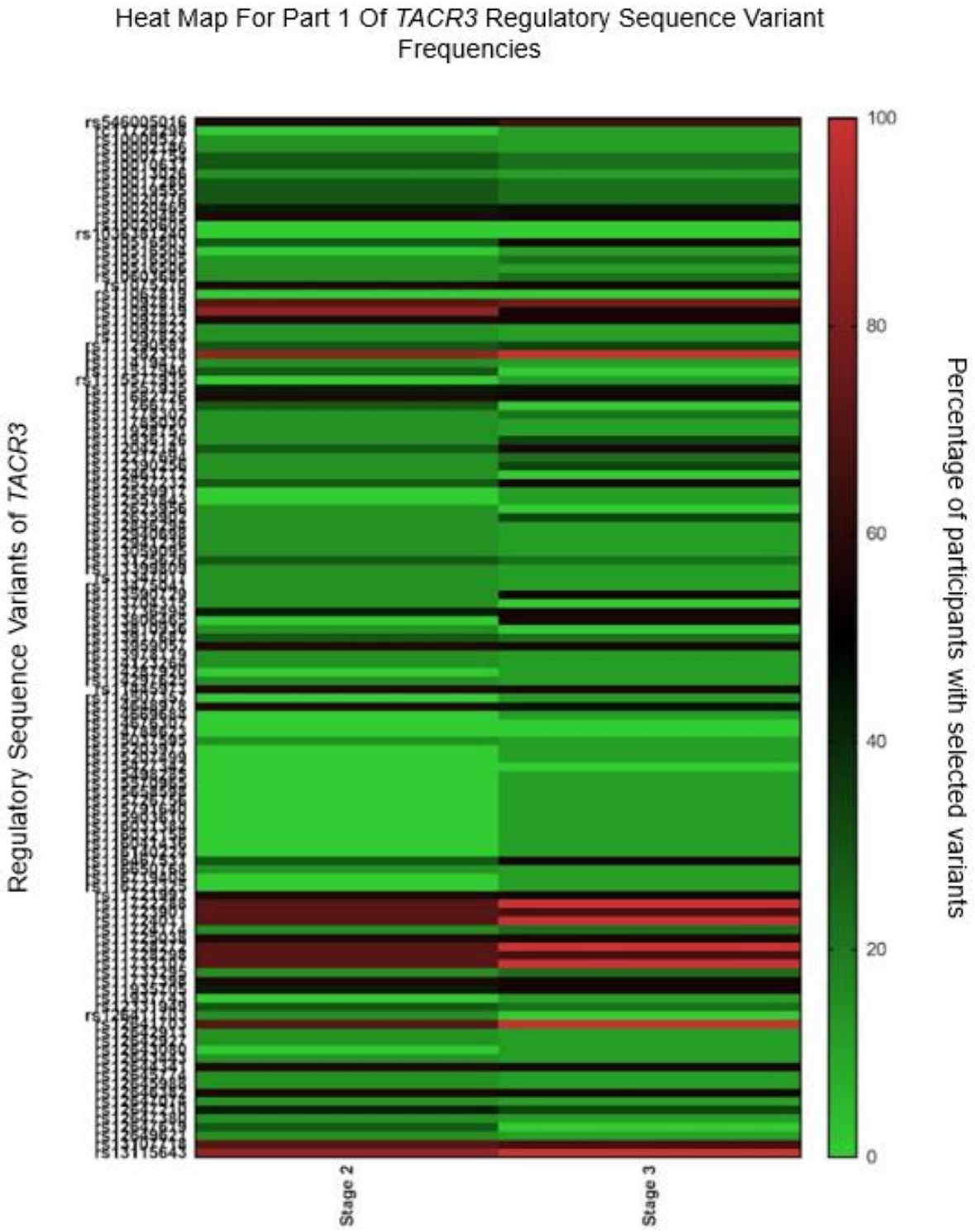
Appendix 2: Heatmap presenting the frequency of *IDO1* regulatory sequence variants in endometriosis stages 2 and 3 in this cohort.



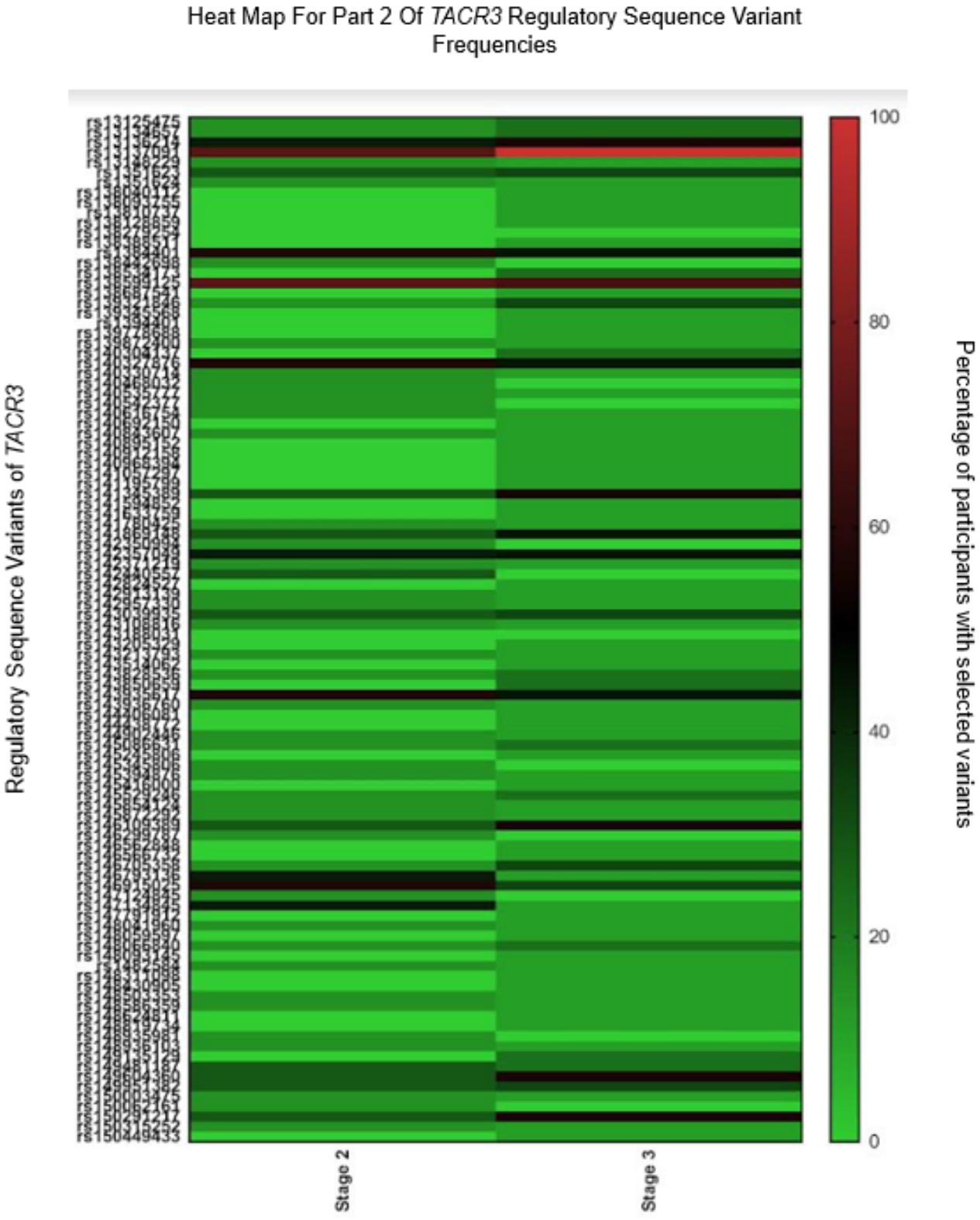
Appendix 3: Heatmap presenting the frequency of *IL-6* regulatory sequence variants in endometriosis stages 2 and 3 in this cohort.



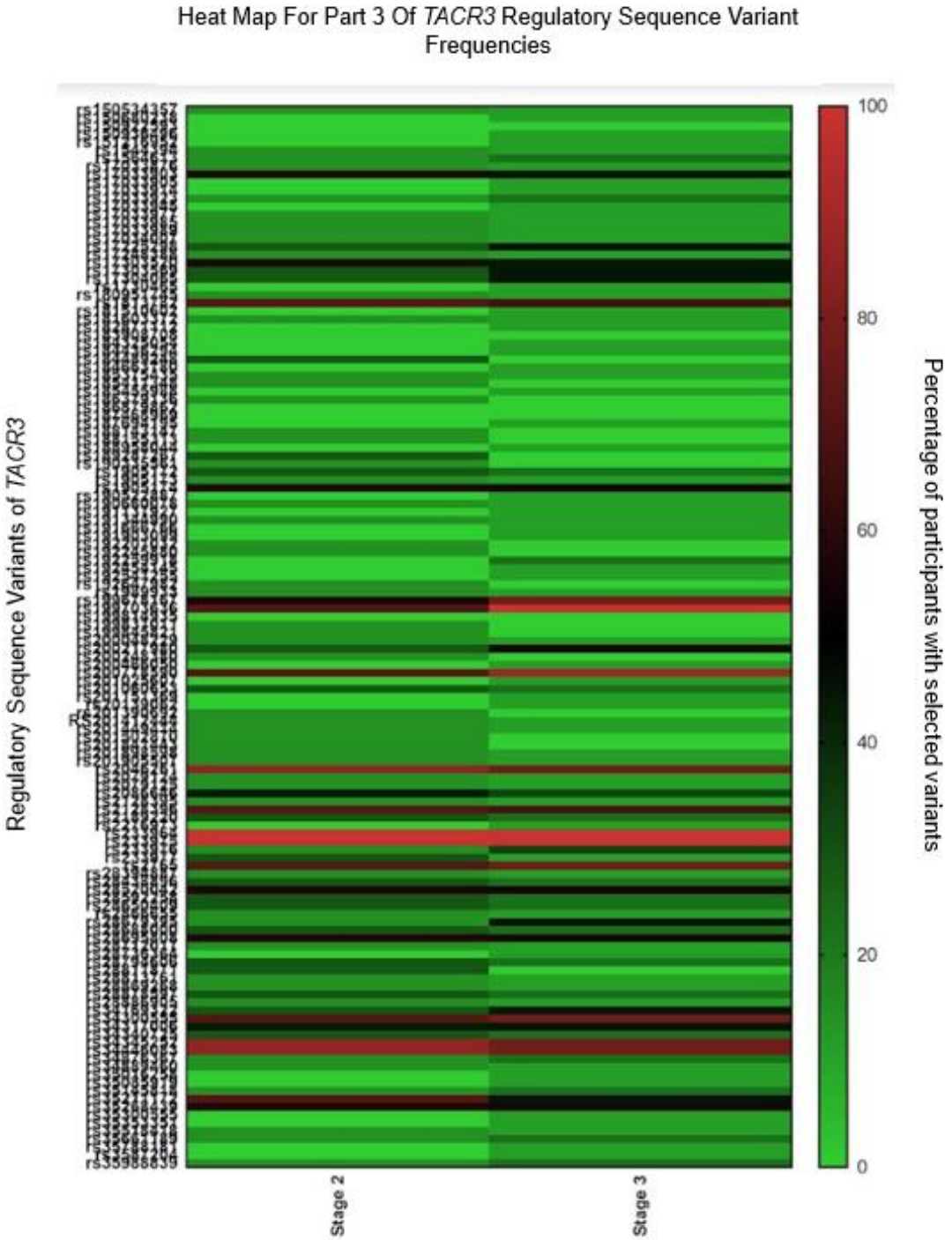
Appendix 4: Heatmap presenting the frequency of the first 121 regulatory sequence variants of *TACR3* found in endometriosis stages 2 and 3 in this cohort.



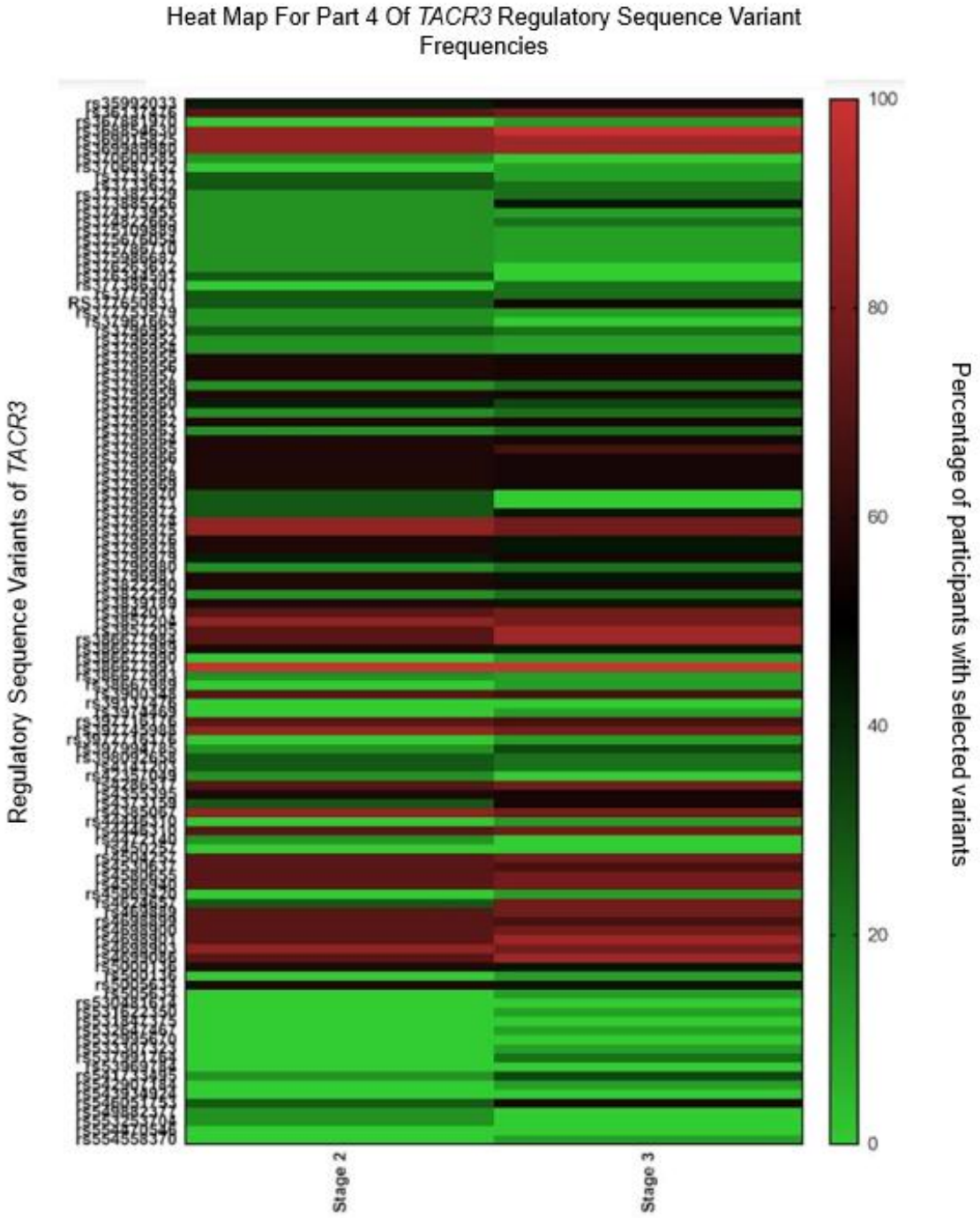
Appendix 5: Heatmap presenting the frequency of the second 102 regulatory sequence variants of *TACR3* found in endometriosis stages 2 and 3 in this cohort.



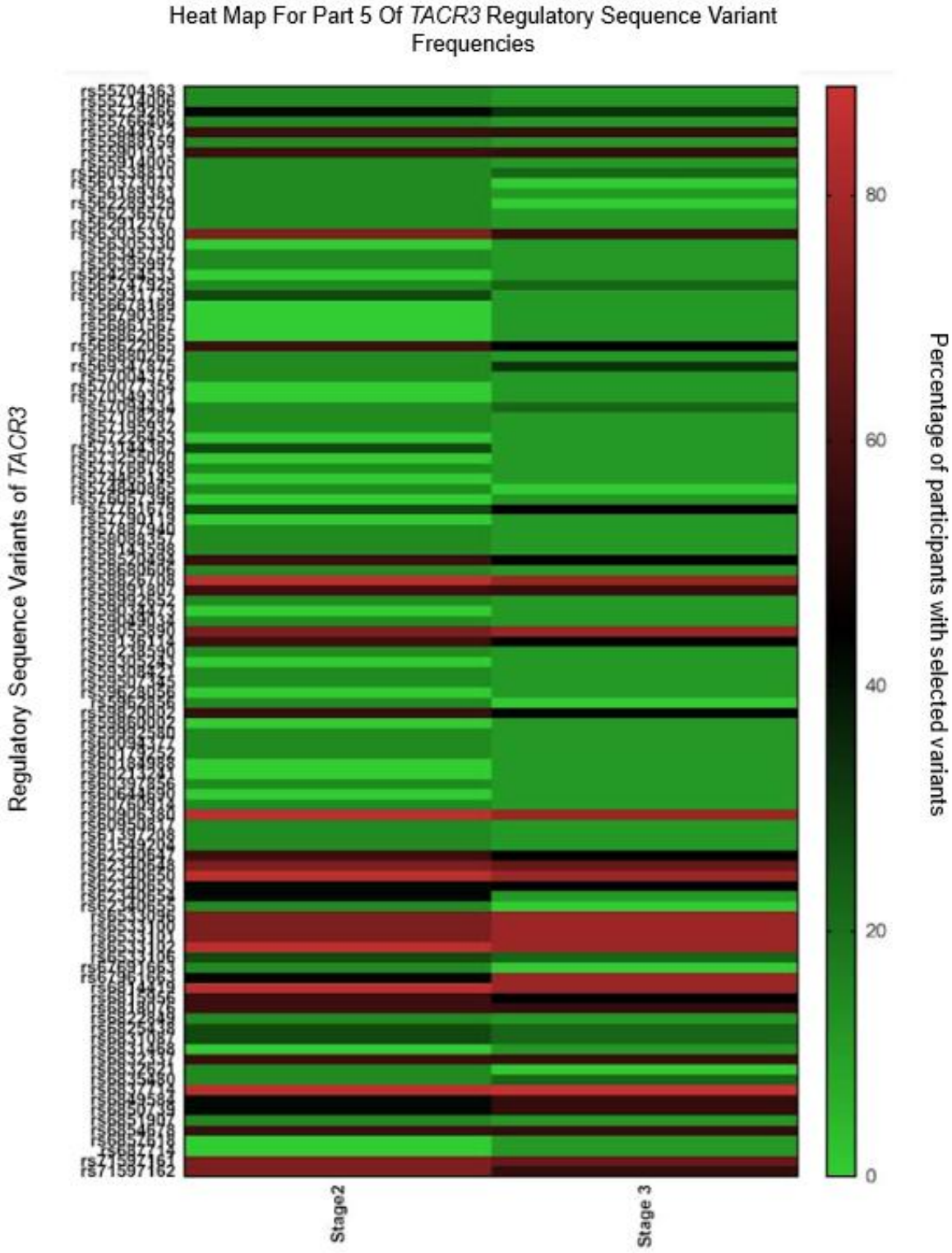
Appendix 6: Heatmap presenting the frequency of the third 112 regulatory sequence variants of *TACR3* found in endometriosis stages 2 and 3 in this cohort.



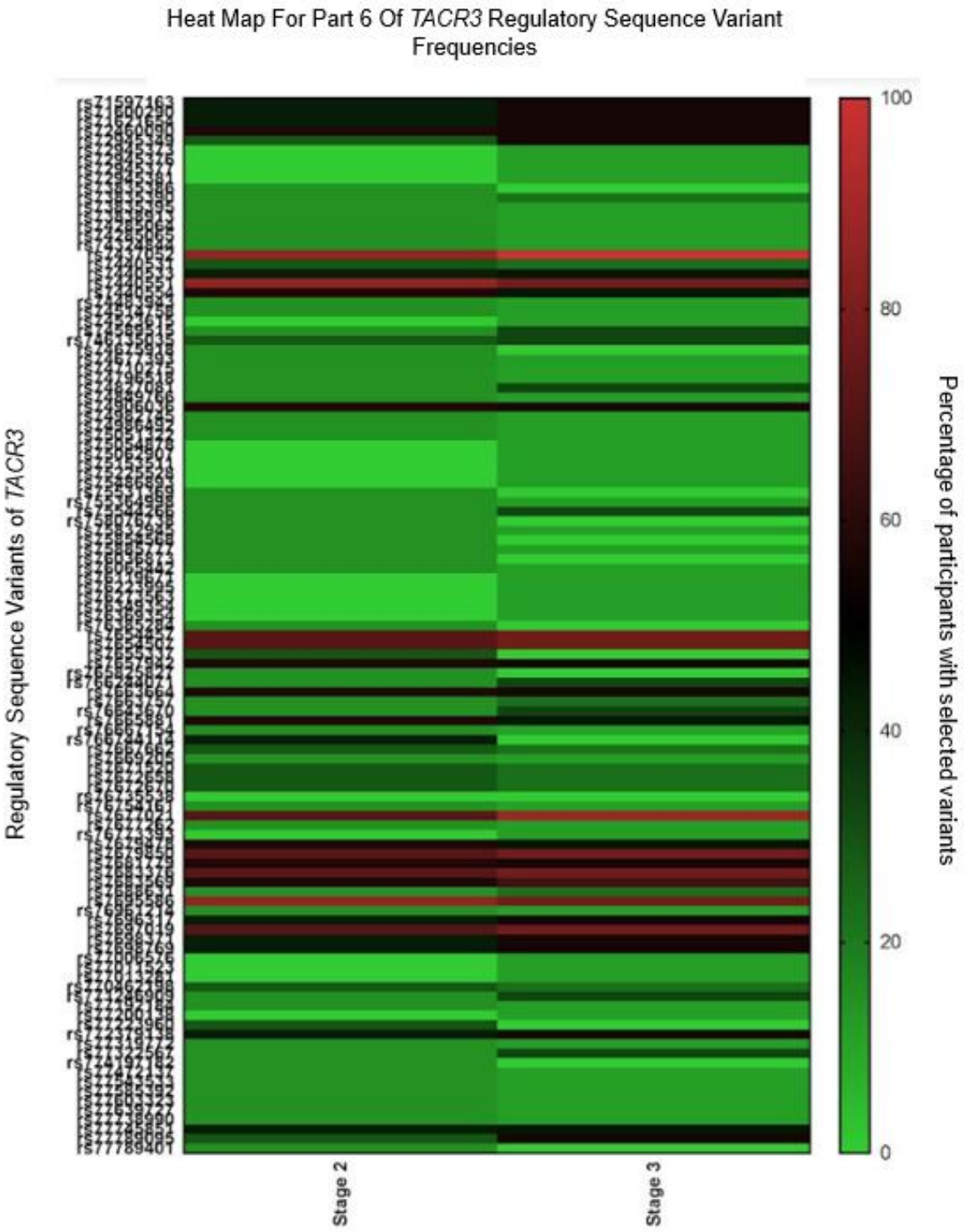
Appendix 7: Heatmap presenting the frequency of the fourth 115 regulatory sequence variants of *TACR3* found in endometriosis stages 2 and 3 in this cohort.



Appendix 8: Heatmap presenting the frequency of the fifth 115 regulatory sequence variants of *TACR3* found in endometriosis stages 2 and 3 in this cohort.



Appendix 9: Heatmap presenting the frequency of the sixth 111 regulatory sequence variants of *TACR3* found in endometriosis stages 2 and 3 in this cohort.



Appendix 10: Heatmap presenting the frequency of the seventh 84 regulatory sequence variants of *TACR3* found in endometriosis stages 2 and 3 in this cohort.